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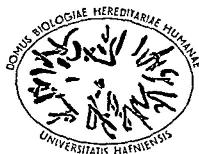
MYOTONIA

Thomsen's Disease (Myotonia Congenita), Paramyotonia, and Dystrophia Myotonica

A Clinical and Heredobiologic Investigation

by

EIVIND THOMASEN



1948

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PREFACE

In 1938, during my work at the Outpatients' Department in the Orthopedic Hospital, Copenhagen, I came across my first patient with myotonia. In the following years I succeeded in tracing a number of other persons presenting the same symptom. During my period as assistant in the Neurological Department of the Kommunehospital, Copenhagen, its Chief Physician *K. H. Krabbe*, M.D., suggested that I continued my investigations of affections with myotonia which had not received any thorough treatment in Scandinavian medical literature. I am grateful to Dr. Krabbe for his encouragement, his amiable assistance and keen interest in my work.

The heredobiological investigations were carried out in The University Institute for Human Genetics, Copenhagen. I here received valuable help, and for this I am indebted to its chief, Professor *Tage Kemp*, M.D., whose guidance and stimulating support has been a great help.

The electromyographical investigations were made for me in the Department of Physical Medicine, in the Kommunehospital, Copenhagen, and in the Institute of Neurophysiology, University of Copenhagen. I thank the heads of the two departments, Chief Physician *Svend Clemmesen*, M.D., and Director *Fritz Buchthal*, M.D., for their personal assistance, and Dr. Buchthal for his help in the preparation of the chapter on Electromyography.

I would also offer my thanks to Professor *Harald Okkels*, M.D., University Institute of Medical Anatomy, and to *Harald Gormsen*, M.D., University Institute of Forensic Medicine, Copenhagen, who assisted me in the histological examinations.

Eye examinations, and especially by slit lamp, were carried out in various Copenhagen hospital wards as well as by a number of oculists throughout the country. I thank the chiefs and staffs of the departments as well as the oculists for their ready assistance. I should extend my special thanks to *Viggo A. Jensen*, M.D., and to *B. Lavaetz*, M.D.

Several of my patients have been admitted to hospital wards where examinations for my special purpose were made. It is my pleasant task to thank the chiefs of the various wards and departments for their kind admission to case records and for their helpful assistance.

Finally, I offer my thanks to the general practitioners I have troub
with inquiries and those that have drawn my attention to new patien
with the affections here dealt with. Special mention must be made o
Chief Physician Haagen Jessen, M.D., Dr E. Hess Thaysen, Gudru
Brun, M.D., and of Chief Physician Georg K. Stürup, M.D., to whom
I am also indebted for his kind assistance in the preparation of the section
on Mental Changes.

My patients and their relatives have always been kind, understanding and obliging — also when requested to undergo special examinations, and I will remember them with gratitude.

Financial aid towards the present work was granted me by the *Guildal Fund* and by the *P. Carl Petersen Fund*, and I wish here to express my obligation and gratitude

Aarhus in April, 1948.

Eivind Thomasen.

CONTENTS

CHAPTER IV

CHAPTER V

CHAPTER VI

CHAPTER VII

CHAPTER I

INTRODUCTION

In 1876 myotonia was described as a specific symptom by Asmu[s] Julius Thomas Thomsen, a physician, who himself suffered from myotonia.

Myotonia is localized to the striated musculature. It manifests itself by a protraction of a strong contraction, and is accompanied by characteristic electrical phenomena in the musculature

Myotonia is the common symptom of the diseases which are being treated in the present paper: Thomsen's disease, paramyotonia, and dystrophia myotonica, all three are hereditary

Thomsen's disease is a purely muscular syndrome with myotonia and more or less pronounced muscular hypertrophy

Paramyotonia is almost identical with Thomsen's disease. The myotonic phenomena are, however, especially pronounced after reduction in temperature

Dystrophia myotonica, on the other hand, is first and foremost characterized by dystrophies, partly muscular and partly non-muscular, while the myotonia, generally, is of secondary importance

A number of non-hereditary cases have been reported under the designation of myotonia acquisita During later years, however, doubts have arisen as to the justification of this conception.

The majority of reports hitherto published on these diseases are of a casuistic nature, and outside the textbooks there are no works dealing with all the above-mentioned diseases Therefore, a satisfactory comparison has been impossible

Some authors still refer to the diseases with myotonia here discussed as rare of occurrence, but there is no doubt that the Zurich ophthalmologist, *Vogt*, is right when he writes about dystrophia myotonica: "Once one is acquainted with this disease, one keeps on finding new cases." There is a striking increase in the number of patients alongside the growing interest in and knowledge of the diseases. As an example may serve the fact that before 1938 there were only three Danish reports of patients

2 to give a clinical description of the pathological pictures of Thomsen's disease, paramyotonia, and dystrophia myotonica with a particularly detailed description of the non-muscular dystrophies;
3 to investigate the influence of these diseases on the social conditions of the patients, with a special view to the importance of the mental changes to the social deterioration in cases of dystrophia myotonica;
4 to discuss the justification of maintaining the term myotonia acquisita,
5 to give a description of a special syndrome—classified as a special form of Thomsen's disease—with myxedema, muscular hypertrophy, and functional disturbances of the muscles, resembling myotonia;
6 to investigate the heredity of Thomsen's disease and dystrophia myotonica in five and in twenty-one families, respectively,
7 to discuss the results of these investigations with the object of ascertaining whether Thomsen's disease (including paramyotonia) is identical with dystrophia myotonica, or whether these groups of diseases can be characterized as being well defined and genetically different

BIOGRAPHY OF DR THOMSEN

Asmus Julius Thomas Thomsen was born on July 19th, 1815, at Brunsholm Manor on the Angel Peninsula, South Slesvig, which was then Danish territory

Dr Thomsen's father was Jensenius Thomsen, the owner of the manor His mother, Henriette Nicoline von Barner, was a daughter of Tugendreich Julius von Barner, Danish major and customs superintendent, Knight of the Order of the Dannebrog

Thomsen studied at the Danish universities of Kiel and Copenhagen and graduated from Kiel In 1839 he defended his doctorate thesis, entitled De dipsomania In the same year he set up as a practitioner, and in 1853 he became medical officer in Kappel, near the town of Slesvig

During his earlier life Dr. Thomsen wrote, apart from his thesis, several minor reports on various infections, on abortives, and on disease and health conditions in Iceland and the Faroe Islands. Strangely enough, he also published an article on cinchonium sulphuricum, which has later been proved to be an effective drug against myotonia.

In 1864 Prussia conquered Slesvig from Denmark, and the 49-year-old Dr Thomsen thus became a German subject.

His reason for publishing, in 1876 at the age of 61, the treatise on myotonia was the fact that the Prussian army medical officers refused to accept a certificate of the disease in one of his sons. The title of the

with Thomsen's disease and none of dystrophia myotonica. In the course of a few years I succeeded in finding twenty-nine patients with Thomsen's disease and one hundred and one with dystrophia myotonica.

Erb's monograph from 1886 is the only thorough clinical work on Thomsen's disease. Paramyotonia has been treated in casuistic reports only, but dystrophia myotonica has clinically been dealt with by authors of several greater works, of whom must be mentioned *Steinert* (1909), *Adie & Greenfield* (1923), and *Rouquès* from 1931. During recent years *Ravin* and co-workers have published a series of more detailed clinical investigations on dystrophia myotonica, but the material offered by these authors is always found to be comparatively limited.

None of the works on the heredity of Thomsen's disease deal with a greater number of families. The works on the occurrence of the disease in Dr. Thomsen's own family were written by *Thomsen* in 1876 and by his grand nephew, *Nissen*, 1923. *Erb* did not treat of the question of heredity, which has only been discussed casuistically. The heredity of paramyotonia has received casuistic attention, and special mention must here be made of *Sander's* report from 1935. The heredity of dystrophia myotonica has been especially investigated by ophthalmologists, who have taken an interest in the disease because of its typical, heritable cataract. *Fleischer* and *Vogt* have supplied material for heredobiological investigations by *Henke & Seeger* (1927), and *Frey* (1925), respectively. Further, among the greater works on heredity, attention must be called to *Boeters'* treatise on myotonia in Silesia (1935). He found patients with Thomsen's disease and dystrophia myotonica mixed in the same families, and did not, therefore, consider any genetic difference between the two diseases. *Maas & Paterson* (1939) have collected considerable material in respect of patients in London, and they were of the opinion that Thomsen's disease, paramyotonia, and dystrophia myotonica are identical, as the two former can only be regarded as variants of dystrophia myotonica According to their view it would be possible to find in the families concerned, cases that could be diagnosed as Thomsen's disease, together with cases of obvious dystrophia myotonica In reality they held, like *Boeters*, that there is no genetic difference.

For prognostic and eugenic reasons it would be of great theoretical and practical importance to arrive at a solution of the problem that thus arises: Is Thomsen's disease (including paramyotonia) identical with dystrophia myotonica, or are we dealing with different nosologic groups, clinically as well as genetically?

The purpose of the present work is:

1 to give a clinical and physiopathologic description of myotonia with a discussion of the cause and treatment of this symptom;

CHAPTER II

MYOTONIA

Myotonia is the characteristic symptom of the hereditary diseases: Thomsen's disease, paramyotonia, and dystrophia myotonica It is a peculiar functional disturbance of the striated musculature, characterized by an abnormally protraction of the muscle contraction accompanied by characteristic electrical phenomena in the musculature whereby the relaxation does not, as is normal, take a fraction of a second, but many seconds, during which the contraction subsides gradually (Fig 1)

By way of introduction to a clinical and heredobiological description of these diseases, the present chapter is devoted to a clinical and physiopathologic description of myotonia as well as of its treatment

A CLINICAL INVESTIGATIONS

Earliest Manifestation

Myotonia is the symptom which most frequently becomes manifest, but there is a definite difference in the ages at which the myotonia in Thomsen's disease (including paramyotonia) on the one hand, and dystrophia myotonica on the other, manifests itself.

In Thomsen's disease and paramyotonia, myotonia is often congenital, as the symptom may be shown to be present in new-born infants It here manifests itself in the form of suckling difficulties, Graefe's sign, and protracted contraction of the orbicularis oculi when washing the face with cold water [*Thomsen* (1876), *Friis* (1891), *Nissen* (1923), and *Kiehl* (1939)] As a rule, however, myotonia in these diseases manifests itself in early childhood, and the first symptoms are often observed when the child is to begin walking In some cases myotonia does not become evident until school age, but rarely after puberty.

I have not in my own material found myotonia manifested in infants, and none of the parents have observed myotonia in the children until they began to walk. Most frequently the myotonia manifested itself in early childhood: at the age of three to four years.

treatise was: "Tonische Krämpfe in willkurlich beweglichen Muskeln in Folge ererbter psychischer Disposition (Ataxia muscularis)".*)

Dr. *Thomsen is described as a good physician and an amiable, modest* man with marked gifts as a lyrist. He translated a number of Danish poems into German and was himself author of a number of lyric poems and songs [*Ebstein* (1929)]

After a long life in medicine Dr. Thomsen died at Kappel on February 3rd, 1896. He was married and had five sons and one daughter.

SYMBOLS OF THE GENEALOGICAL TABLES

- □ Normal male
- ○ Normal female
- □⌒□ Enzygotic male twins
- □⌒○ Binovular twins
- ◇ Normal siblings, *i e* brothers and sisters
- △ Normal persons of unknown sex
- ⊠ Male died in childhood
- • Miscarriage or stillbirth of unknown sex
- ⊠ Insane or mentally deficient male
- ◧ Male with cataract
- ◧ *Male presumably suffering from Thomsen's disease or dystrophia myotonica*
- ◳ Male with suspected Thomsen's disease or dystrophia myotonica
- ■ Male with Thomsen's disease or dystrophia myotonica

*) "Tonic cramp conditions in voluntarily movable muscles, caused by inherited psychical disposition (Ataxia muscularis)"

of men while conscripted have been punished because of myotonia, which e. g. made them unable to raise their hand to salute or free their finger from the trigger of their rifles In the present age of automatic weapons this might have disastrous consequences. [*Peters* (1879), *Rieder* (1884), *Andersson* (1904), *Pesme* (1911), *Michaud* (1915), and *Severin* (1916)]. *Angell* (1891) had a patient with Thomsen's disease, who was forced into military service, and finally shot himself because of his great sufferings

(1) *Localization*

Myotonia is comparatively rarely present in the *facial muscles*, and, as a rule, only in cases of Thomsen's disease and paramyotonia It is most marked in the orbicularis oculi after having firmly closed the eyes the patient finds it difficult to open them again This particular symptom may often be provoked by a cold washing of the face and is described as characteristic of paramyotonia In this disease it may be caused by a blast of cold air In the *ocular muscles*, heavier myotonia may be found to hamper the mobility of the eyes, and, as already mentioned, Graefe's sign may be a myotonic symptom

The *mastication muscles* are very often found to be the seat of myotonia, also in dystrophia myotonica After biting hard, the patient finds it difficult to open his mouth, and mastication proceeds only slowly. The *tongue* is a frequent seat of myotonia, whereby speech and swallowing may be disturbed Some of my patients also found that the *throat muscles* kept the food back for a time, before it passed into the esophagus

The *respiratory* muscles in their ordinary movements are not hampered by myotonia, but may be in deep breathing and coughing One of my patients, who suffered from emphysema, at times experienced asthmatic respiratory troubles as a consequence of the myotonia The myotonia was especially evident to the eye in the abdominal musculature

Active myotonia of the *upper extremities* is almost constantly present in the finger flexors, after a strong clenching of the hand, the fingers will remain in a bent position for several seconds before they can be straightened slowly In attempts at straightening their fingers the patients frequently make athetoid movements of arms and hands. In more serious cases with active myotonia also in the finger extensors, all movements of the fingers are hampered, and the fingers are moved as in dough. Active myotonia in the muscles of the upper arm and shoulder appears only in severe cases of Thomsen's disease

Active myotonia in the *lower extremities* is present especially in Thomsen's disease and is comparatively rare in dystrophia myotonica Because of myotonia in the flexors and extensors of the knee, the patients have difficulty in walking when they have been sitting on a chair for

In dystrophia myotonica, myotonia is often the first symptom, but according to the literature on the subject the symptom does not, generally, appear until an adult age — twenty to forty years. Up to now the earliest manifestation has been found by *Maas & Paterson* (1943) in a child of three years.

In my own material, the age of manifestation of dystrophia myotonica averaged 19.7 years. The earliest manifestation of myotonia in this disease I found in a boy aged two, who displayed mechanical myotonia. At the age of four he also displayed active myotonia

Myotonia remains a symptom for the rest of the patient's life, although the degree of manifestation may vary. In dystrophia myotonica, the muscular dystrophy may render demonstration of myotonia impossible.

Form of Manifestation.

Myotonia manifests itself regularly with symmetrical localization in the striated musculature — in Thomsen's disease and paramyotonia most often spread almost universally, and in dystrophia myotonica most frequently localized in certain muscle groups. Myotonia has never with certainty been demonstrated in the muscles of the sphincter ani externus or the sphincter urethrae membranaceae.

Myotonia following a voluntary muscle contraction is called active myotonia, when following a contraction caused by mechanical or electrical stimulation, it is, respectively, termed mechanical or electrical myotonia.

ACTIVE MYOTONIA

This symptom is described by the patients as cramp or stiffness in the muscles The word "myotonia" was unknown to *Thomsen* (1876), who described it as "tonic cramp condition in voluntarily movable muscles " The stiffness is most noticeable in hands and legs, and may hamper their normal functioning Thus, the patients may find it difficult to let go after a strong hand-shake or to release their grip on a tool; farmers regularly complain of being unable to milk. Stiffness of the legs makes walking slow and staggering, and sometimes the patients are only able to move their legs like rods, especially when going up stairs.

Frequently this peculiar stiffening of movements in muscularly strong persons has been regarded as simulation, and there is a number of reports telling of how army doctors were mistaken in this respect. The first known mistake caused Dr. *Thomsen* (1876) to describe the disease The military authorities refused to regard his certificate of the ailment in one of his sons, who had been called up for military service. A number

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some time. In severe cases they move their legs like rods, and in milder cases they move as if walking in water.

(2) *Consistency etc. of Myotonic Muscles.*

When completely relaxed the consistency of the muscles is as in normal muscles. In extremely severe cases of Thomsen's disease the patients may have difficulty in relaxing, and in such cases the muscles will practically always be more or less tensed.

The passive movements are not hampered except in the above-mentioned severe cases of Thomsen's disease. Any increase of tone in the ordinary sense is not found.

During the retarded contraction the patient may notice a certain *tension in the muscles. Pains are never felt.*

(3) *Relation of Myotonia to Exertion*

Myotonic patients may often play the piano without difficulty, but they will experience a protracted contraction if attempting to wring a cloth Active myotonia is necessarily conditioned by a certain, not too feeble, exertion during muscular contraction, a phenomenon, which *Leyden* (1874) has described in a patient, presenting unquestionable myotonic symptoms The effort necessary is, as a rule, less in cases of severe myotonia, and in the most severe cases it is so slight that almost any movement may cause active myotonia

The duration of the protracted contraction, and thus the degree of active myotonia, is to a certain extent proportional to the force employed, but an excess force beyond a certain limit will involve no further protraction of contraction.

(4) *Gradual Disappearance of Myotonia through Repetition of Movements.*

A repetition of the muscle contraction with the necessary force immediately upon completion of the delayed contraction will, as a rule, cause another protracted contraction. But this time it is of shorter duration, and *this is more and more evident* as the movements are repeated, and the muscle contractions will eventually subside with what appears to be normal speed. The number of muscle contractions necessary to eliminate the active myotonia can in practice be used as a measure of the degree of myotonia in the muscles in question.

As a rule, fingers can be moved freely after seven to ten firm clenchings of the hand, and free walking is possible after about ten steps, but it may take more to work off active myotonia. Adult patients gradually get in the habit of keeping the muscles in constant movement, thereby keeping the period of relaxation down.

J Thomson's patient, a six year old child, hit the nail on the head when compar its own myotonic symptoms with the way in which a train starts "It will go all harder, when it gets started, just like me "

Dr Thomsen described his own myotonia in childhood in these terms "Once machine had got going, I was just as active as any other boy of my age," and two my patients of the Thomsen family, with comparatively severe diffuse myotonia a well-developed muscles in their younger days were trapeze acrobats in a circus Bef every performance they had to stand behind the curtain and make energetic moveme in order to "work up steam" Then it was possible for them to run into the arena a do acrobatics on rings and the trapeze

In the most severe cases of Thomsen's disease the patients canr completely work off active myotonia, but in milder cases, on the cc trary, it is necessary for the muscles to have rested for ten to fifte minutes before being examined for active myotonia.

Ravin (1939) has demonstrated how a protracted, strong tetanic cc traction is of the same effect as repeated contractions. Some of my seve cases of Thomsen's disease could, by a forceful contraction of the l muscles for one and a half to two minutes, completely eliminate t active myotonia, thus enabling themselves to walk freely from the ve first step Following contractions of shorter duration a more or le retarded relaxation remains

(5) *Influence of Temperature on Active Myotonia*

The influence of heat on active myotonia was observed by *Thoms* (1876), who found it easier to move in hot than in cold temperatur *Yealland* (1923) has described a patient who felt no active myotonia long as he stayed in India

The influence of cold is even more evident, and especially humid co may aggravate active myotonia Some of my patients with milder degre of myotonia only noticed their active myotonia after being subjected cold The influence of cold on active myotonia is particularly pronounc in the so-called paramyotonia

Some authors have found active myotonia in their patients unaffect by cold [*Kumagai* (1913)] In several of my own patients with Thor sen's disease I made the same observation, and in others I have, li *Strumpell* (1881), noticed that cold as well as heat aggravate the conditio

Ergographic tests made by *P. Jensen* (1903) revealed that the co traction and protraction phases were shorter when heating was effect as is the case in poikilothermal animals *Nylin* (1926) and *Ravin* (193 found active myotonia to be of longer duration in higher temperatur but the increased force of the antagonists is still greater, with the resu that the protraction of contraction appears to be shorter after subjecti to heating The weakening of the muscles in cold is particularly notic

able in paramyotonia, where the muscles may remain paretic for a longer period after cooling.

In one of my patients with a severe case of Thomsen's disease I cooled one hand and forearm in water of 7 to 8 degrees Centigrade. After ten minutes the patient was able to work off the active myotonia by only two clenchings of the hand as compared with a previous eight. The myotonia in the other hand was unchanged. Controls on the other hand gave similar results.

Ravin (1939) investigated whether changes in active myotonia on cooling might be linked with the blood circulation. Using a blood pressure cuff he produced venous congestion and ischemia of the forearm and hand, but without any change in the active myotonia.

(6) *Influence of other Factors on Active Myotonia.*

Physical fatigue, as well as hunger, aggravates active myotonia.

The influence of psychical factors was observed by *Thomsen* (1876). My patients especially stressed that vexation and fear aggravated active myotonia

As a result of sudden fright, or after a sudden movement of self-protection, e g. when the patient happens to stumble, the active myotonia in severe cases of Thomsen's disease may set in at once in all muscles with the result that the patient remains as rigid as if petrified for about a minute, and falls without being able to prevent himself.

Ballet & Marie (1883) and *Klein* (1939) reported that sexual abstinency had an aggravating effect on active myotonia, but I have not from my patients been able to collect information confirming this point.

The aggravating influence of menstruation on active myotonia has been described by *Lord* (1900) and *Stattmüller* (1923), and I observed the same effect on two of my patients with severe degrees of Thomsen's disease. In one of these the active myotonia further grew worse towards the end of a period of pregnancy, as had also been described by *Gardiner* (1901), *Stattmuller* (1923), and *Berkmann* (1935).

(7) *Variation in Active Myotonia with Growing Age.*

Thomsen (1876) wrote of his own myotonia that it was seemingly worst in childhood and caused him less trouble as the years passed. He did, however, to a certain degree ascribe this observation to the fact that he gradually learnt to counteract the active myotonia by keeping his muscles in constant function.

Kiehl (1939) found the active myotonia to be worst in puberty — an observation I have made in several of my female patients with Thomsen's disease.

There are several reports of improving myotonia with increasing age: *Cook & Sweeten* (1890), *Stattmuller* (1923), and several others. In several of my patients it was evident that active myotonia was on the decrease with the increase of age, it did not, however, disappear. It is quite a different matter that the patients, as stated by *Thomsen*, gradually learn to fight the ailment In patients with dystrophia myotonica, the myotonia soon reaches a certain degree, which remains constant, unless it grows less pronounced because of muscular dystrophia.

(8) *The so-called "Paradoxical Myotonia".*

This designation covers the phenomenon observed when active myotonia increases on the first repetitions of movement and only after the second and following contractions begins to decrease *Ravin* (1939) opined that the myotonia in the antagonists caused an increase in strength on the second contraction with consequent longer subsiding period, and so on until the limit of the influence of the strength had been reached.

(9) *Ergograph Registration of Active Myotonia.*

For this purpose may be used either the usual Mosso's ergograph or, as did *Kramer & Selling* (1912), a device with a pair of Marey's tambours

When applying the Mosso ergograph the weight may cause a passive extension during the period of relaxation, the registration of which thereby becomes inaccurate To avoid this drawback I constructed an apparatus in which the weight is put out of operation during the relaxation period and only a slight weight keeps the string taut in other words an energy storing device The third finger was used for registration of the curves

As an illustration of the active myotonia a curve is shown, registered by a patient who was a severe case of Thomsen's disease Upon the command "Let go", it took four or five seconds before the subsiding was complete (Fig. 1)

Finally, the figure shows the registration of a series of consecutive contractions in the same patient, who had great difficulty in relaxing completely Thus the first contraction was somewhat hampered by a tension in the antagonists. The second was smaller than the first contraction and the contraction phase even more hampered by myotonia in the antagonists Not until the third contraction was the myotonia on the decrease in flexors as well as in extensors the contraction phase became normal and subsiding shorter The myotonia apparently disappeared after a few more contractions

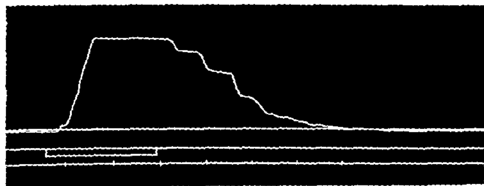




Fig 1

Ergogram from patient with severe Thomsen's disease

Upper figure Protracted contraction Duration of voluntary innervation appears from second line from bottom
Lower figure Series of contractions in same patient Second and third *contractions* are *supposedly* weak on account of myotonia in antagonists At sixth contraction the *protractions* have *disappeared*

MECHANICAL MYOTONIA

A percussion hammer stroke on a normal muscle will produce a rapid contraction of a bundle of muscular fibres, with a subsequent rapid subsiding In lean patients a furrow-shaped, rapidly disappearing concavity can be observed on the surface of the muscle

In some, especially in lean, persons it may not infrequently be observed that on the percussioned spot a small swelling appears, independent of the rapid contraction of the muscle bundle The swelling remains for several seconds, at times for half a minute, and is hard, but not tender. The area of the swelling corresponds to that of the percussor and stretches across a number of muscle bundles. This reaction upon mechanical stimulation is termed the *idiomuscular reaction*

In muscles of patients with myotonic symptoms it can be observed that the contraction of the percussioned muscle bundle remains for several seconds after the stimulation This reaction is called *mechanical myotonia.*

(1) *The Idiomuscular Reaction*

This reaction has no connexion with myotonia, but in medical literature there are frequent examples of authors who either mistake it for mechanical myotonia or wrongly consider it to be a characteristic myotonic symptom.

The reaction was first observed and described by *Schiff* in 1859, who found it in bared muscles of newly-dead bodies. The Danish physician *R. A. Holm*, in 1872, was one of the first to describe the phenomenon in living, lean patients with pneumonia and typhoid fever. He noticed a ring-shaped prominence when removing his stethoscope from the breast wall of his lean patients. Further, Curschmann (1905) is the author of a critical literary review, and the most recent known work in this field was written by *Leitinger* in 1943.

The reaction is especially easy to demonstrate in thin persons and preferably in flat superficial muscles on a hard foundation. It is often found in thin persons with dystrophia myotonica, but, as mentioned, has nothing to do with myotonia. Support for this view is provided by the electromyographic examinations, made by *Buchthal & Clemmesen* in 1941. They found no action potentials in the prominent swelling on the surface of the muscle.

(2) *Mechanical Myotonia.*

Mechanical myotonia was first observed by *Bernhard* in 1879, and since then it has been noticed in almost all patients presenting myotonic symptoms. In a number of cases, however, the idiomuscular reaction has wrongly been reported as mechanical myotonia.

Upon percussion of myotonic muscles a somewhat increased irritability may be observed in the majority of cases. Percussion of myotonic muscles causes, in the irritated fasciculi, a tonic contraction, which generally appears as a furrow on the muscle surface (Fig. 2), but in a few cases — e. g. as in the platysma myoides — appears as a ridge. On the edge of the tongue may be seen an indentation, which flattens out in four to five seconds.

The tonic contraction is especially easy to observe in the finger extensors. The patient's forearm is held horizontally with hand and fingers hanging slack. Percussion of the extensor digitorum communis results in a rapid stretching of one of the fingers which will not, as normally, drop immediately, but slowly sink to its original slack position in five to ten seconds. In the thenar it is possible to produce a tonic opposition with extension of the metacarpo-phalangeal and interphalangeal joints, lasting from ten to thirty seconds, and the tonic contraction of the tibialis anterior can be observed in the prominent tendon on the anterior side of the ankle joint.

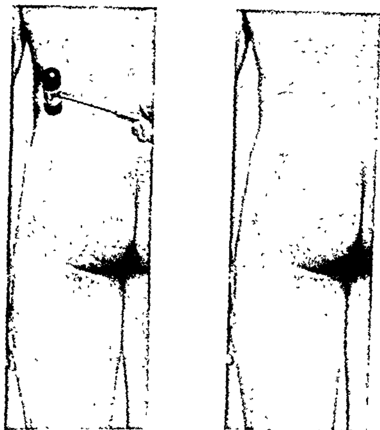


Fig 2
Mechanical Myotonia with clearly visible furrow

In Thomsen's disease the topography of mechanical myotonia often corresponds to that of active myotonia In dystrophia myotonica it is more localized, but not always in the same muscles as the active myotonia. Active myotonia of the forearm is often most pronounced in the finger flexors and the mechanical myotonia in the finger extensors. Mechanical myotonia may in certain cases be demonstrated before the active myotonia becomes manifest. In other cases the mechanical myotonia may be evident even after the active myotonia cannot be demonstrated because of dystrophy of the muscles

Repeated percussions give decreasing mechanical myotonic response, and after two or three percussions it cannot, generally, be demonstrated until after a period of rest.

Bürger & Schellong (1923) found that the mechanical myotonic period was prolonged during subjection to cold, but with strong cooling *Nylin* (1926) observed that the muscles grew paretic and were without mechanical myotonia.

In the examinations of families, I have as a matter of routine examined the patients for mechanical myotonia, localized as mentioned. In one case I found, at the first examination, mechanical but not active myotonia; later the patient also presented active myotonia Observations to the contrary have never been made

Finally, it must be mentioned that mechanical stimulation of the muscle nerves only produces a brief contraction without mechanical myotonia.

ELECTRICAL MYOTONIA

Electrical myotonia is also referred to as *Erb's Sign*, as it was described in particular detail in his classic monograph on Thomsen's disease in 1886

Erb found the nerve irritability to be normal, whereas the muscle irritability was increased Single stimulations seemed to produce normal rapid contractions and relaxations, but *P Jensen* (1903) thought it likely that this contraction might be somewhat protracted, as he was able to demonstrate by rhythmical stimulations — four per second — a kind of accumulation of contraction, never found in normal persons.

Stimulation by tetanigenous, faradic current produced protracted contraction as happens in voluntary contraction In contradiction to the normal effect, a galvanic current through the muscle produced a tonic, sluggish contraction, slowly subsiding after cutting off the current

This sluggish tonic contraction is termed galvanotonus *Erb* discovered that it may be accompanied by undulant movements in the muscle, passing from cathode to anode

Kramer & Selling (1912) found the voltage to be a determining factor as to the duration of the electrical myotonia, which decreased in a series of stimulations and might fail to appear if the patient had made a number of voluntary movements beforehand (*Delprat*, 1892). *Eichler & Hattingberg* (1938) found that electrical myotonia did not appear after a longer period of stimulation with tetanigenous faradic current — as in the case of active myotonia

Cooling had the same effect as in active myotonia [*P Jensen* (1903) and *Nylin* (1926)]

A number of reports tell of investigations of electrical myotonia as directed by *Erb*, and *Maas* (1937) was of the opinion that *Erb's* sign was decisive in doubtful cases

Only in very few cases of hospitalized patients have I made examinations for electrical myotonia In the rest of the cases I have confined myself to examinations for mechanical myotonia. When in doubt I have, as far as possible, arranged for electromyographical examinations.

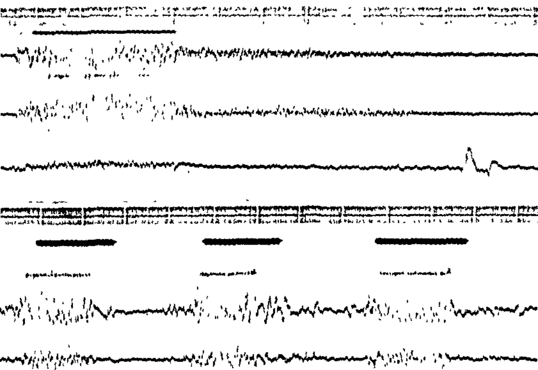


Fig 3

Electromyogram from patient with myotonia 3 concentric needle electrodes in biceps brachii muscle Time intervals 10 *milliseconds* (*Buchthal & Clemmesen*)

Upper figure Voluntary contraction with strong interfering electrical activity after discontinuation of innervation interfering activity with lower gradually decreasing amplitude
Lower figure Myotonic, interfering activity faded away after 10 successive contractions

after-activity was somewhat smaller than during the voluntary innervation, and it decreased gradually The intensified electrical after-activity, demonstrated by *Denny-Brown & Nevin* during the myotonic phase, was not observed

Like a number of previous investigators, *Buchthal & Clemmesen* did not find any difference between the electrical activity and after-activity in patients with dystrophia myotonica as compared with patients with Thomsen's disease

In a number of patients with myotonia, impossible to demonstrate clinically in the muscles of the lower extremities, they found rest-activity and electrical activity corresponding to the mechanical myotonic reaction This observation implies that the functional disturbances may be traced electrophysiologically more widely spread than can be demonstrated clinically

containing some of the results of these investigations and a discussion as to the localization of the cause of myotonia.

For leading-off were applied concentric needle-electrodes connected to an amplifier with a time constant exceeding 1/25 sec. For the registration was used an electrostatic oscillograph with a natural period of 3000 cycles per sec. and a loud-speaker. The leading-off was invariably carried out simultaneously from three places, and the three registrations were made parallel on a strip of photographic paper. In certain cases the movement was also registered through a special device.

As a special feature of myotonia — to an extent almost reaching pathognomy — were found a spontaneous rest-activity in the form of intermittent "showers" of electrical potential oscillations lasting a few seconds. In certain cases the frequency was rapid, but decreasing, whereas in other cases it was slower, but increasing. These showers were heard as characteristic sounds in the loud-speaker, like the growling of a dog. Besides these showers there were a number of single potential oscillations, sounding like cracks in the loud-speaker with intervals of from one half to one third of a second.

As it was possible to demonstrate this changing spontaneous rest-activity through one single electrode without simultaneous demonstration through the other two, the conclusion must be that the activity originates from small sections of the muscle, as the electrodes are generally placed at distances of a few centimetres.

As in the goat muscle preparations (*Brown & Harvey*), the *muscle irritability was strongly increased*; thus, a light touch of the needle electrode was sufficient to produce a lively electrical activity lasting for several seconds. Percussion of the muscle near the electrodes might produce electrical activity corresponding to the mechanical myotonic reaction. Upon the percussion followed a series of single oscillations, which had an extremely rapid initial frequency of 100 to 150 per second (shower). It quickly slowed down, however, to 20 to 10 per second, and the oscillations stopped after some seconds. The reaction was local, as the other electrodes registered only rest-activity or rest.

During voluntary muscle contraction *Buchthal & Clemmesen* were further able to register strong, electrical activity with interference as in normal muscles, but, as distinct from these, it was impossible to produce anything but electrical activity with interference, even at the slightest possible contractions. As is known, single potentials may frequently be registered at slight contractions of normal muscles. Such demonstration was impossible in myotonic muscles.

During the prolonged contraction following voluntary innervation they were able to register a continuous electrical activity with interference lasting for several seconds, but no observation was made of the interval reported by *Denny-Brown & Nevin*. The amplitude of the electrical

however, demonstrated that the mechanical myotonic reaction was still present although the impulses to the muscles were cut off by lumbar or conduction anesthesia, and *Brown & Harvey* (1939) stated that mechanical myotonic reaction and the accompanying electrical activity could be demonstrated in *denervated*, myotonic goat muscles *Denny-Brown & Nevin* (1941) and *Buchthal & Clemmesen* (1941) made the same demonstrations after conduction anesthesia on patients with myotonia

By intra-arterial injection of potassium chloride in a denervated, curarized myotonic goat muscle, *Brown & Harvey* (1939) could produce a tonic contraction with electrical activity, and this electrical activity was of a nature and duration to indicate that it might have the same origin as the electrical activity during voluntary innervation.

These observations exclude the possibility that myotonia is due to reflex impulses from the central nervous system Its origin must be localized distally to the peripheral motor neuron, and there is much to indicate that the impulses have the same origin as during normal, voluntary innervation

Buchthal & Lindhard (1939) experimenting with lizard muscles were able to affect the motor end-plate direct After curarization they were no longer able to affect the end-plate with acetylcholine, but well with potassium chloride, and this latter affection was the cause of a long contraction produced by repeating impulses with electrical activity

The conclusion of these experiments indicates that the motor end-plate consists of two functionally different sections- a nervous part, which is paralysed by curarizing with normal doses, and a muscular part, which, after curarization, is able to emit normal impulses *Brown & Harvey's* experiments on curarized, denervated myotonic goat muscles with intra-arterial injections of potassium chloride would lead to the conclusion that the repeating impulses in the myotonic muscle originate from the muscular part of the motor end-plate

The motor end-plate is more sensitive to novocaine and quinine than the muscle fibres (*Buchthal*). The disappearance of myotonia following the administration of novocaine and quinine may, therefore, also support the view that the repeating impulses of myotonia originate from the muscular part of the motor end-plate In the myotonic muscles the end-plate must be abnormally sensitive, as it reacts on the voluntary nerve impulse or on electrical and mechanical stimulation by emission of a series of action potentials, and not, as in normal muscles by emission of a single action potential

Buchthal, Honcke & Knappeis have personally communicated to this writer their results of some experiments, not yet published, which form part of an investigation into the mechanical qualities of muscles They have examined isolated, small fasciculi from myotonic goat muscles, and

Buchthal & Clemmesen found that the myotonia after mechanical stimulation and voluntary innervation disappeared if the proprioceptors were paralysed by injections into the muscles of one half per cent solution of novocaine. The voluntary muscle contraction and its electrical activity were unaffected by these injections. The same observations could be made by substituting quinine hydrochloride solution (1 : 30) for novocaine

After blockade of the innervation of the arm by plexus anesthesia, as directed by *Kulenkampff*, the muscles grew paralytic, but it was still possible to produce myotonic reaction, its electrical activity being somewhat stronger than before the blockade. After local novocaine injections into the paralytic muscles the mechanical myotonic reaction as well as its electrical after-activity disappeared.

Mention may here be made of the fact that paravertebral novocaine injections on the sympathetic trunk was of no effect on the myotonia.

When conduction anesthesia was applied to the ulnar nerve at the elbow and to the median nerve near the wrist with paresis of the small muscles of the hand, there was still present a strong myotonia after voluntary innervation of the finger flexors, and the electrical activity was unchanged. Blockade of the radial nerve with paresis of the finger extensors produced no change in the myotonia of the finger flexors.

Examinations of normal persons revealed that a hampering of the finger extension produces a strong contraction with electrical activity in the flexors of the forearm, and in the myotonic patients the electrical after-activity in the flexors was much stronger with higher amplitude if the patient made forceful attempts to extend the fingers. Thus, there seems to be a normal fixation contraction in these muscle groups when the antagonists contract strongly.

Discussion

Gregor & Schilder (1913) and several other previous authors were of the opinion that the prolonged contraction was of a similar nature as in voluntary innervation and originated from the central nervous system through reflexes from the proprioceptors of the muscles.

With increasing quantities of novocaine in the muscle substance (one half per cent solutions), *Buchthal & Clemmesen* (1941) were able to block, first, the mechanical myotonic reaction, and, later, the myotonia after voluntary innervation Following this treatment, which also blocks the proprioceptors, the voluntary contraction was unchanged, and at a first glance this might support the view that myotonia is caused by reflexes through the proprioceptive nerves.

Grund (1919), *Schaffer* (1921), and *Kennedy & Wolf* (1937) had,

Atropine is of no definite effect on myotonia *Weiss & Kennedy* (1924) administered considerable doses of atropine to a patient with general myotonia. Subjectively there was a certain degree of improvement, but at the same time so many inconveniences that the treatment had to be abandoned *Keschner & Finesilver* (1925) and *Bremer & Mage* (1929) were unable to demonstrate this effect, and *Kolb* (1938) found no effect as regards goat myotonia Nor could *Ravin* (1940) by the intravenous injection of 10 mg state any effect on the myotonia

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It has never been possible for me to demonstrate *Denny-Brown & Nevin's* after-spasms in patients not counteracting the myotonia by strong contraction in the antagonists.

It is my opinion that these after-spasms are fixation contractions, produced by the active contraction in the antagonists, and that they are only a normal reaction.

D. TREATMENT OF MYOTONIA

Erb's (1886) experiences with regard to treatment of myotonia were depressing. Treatments with electricity, massage, baths, and drugs had hitherto proved without effect. Only in lighter cases it seemed as if gymnastics had a reducing effect on the hampering of movements.

Gymnastics were further recommended by several authors from *Erb's* time· *Bernhard* (1885), *Bechtereff* (1897), *Wersiloff* (1897), *Nikonoff* (1897), *Braun* (1902), and *Goldenberg* (1914)

One of my own patients — a severe case of Thomsen's disease — had found out that gymnastics could counteract his myotonia, and he had therefore made up his own system, according to which he thoroughly exercised all his muscles every morning.

There is a connexion between the effect of gymnastics and the gradual disappearance of myotonia by repetition of movements. Once the myotonia has been reduced to a degree which allows the patient to move comparatively freely, he finds it easier to keep the myotonia away by constant activity.

Alcohol has a reducing effect on myotonic hampering of movements. *Danillo* (1886) was the first who described this effect which is a common experience among patients with myotonia. One of my extremely severe cases of Thomsen's disease enjoyed considerably greater freedom of movement following the assimilation of alcohol. After a dinner with wine he could even go so far as to dance without restraint.

A considerable number of drugs have been brought into use against myotonia With the literature on this subject as a basis I shall briefly mention the results of these experiments of treatment

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8.4 to 1 6 seconds, but despite repeated treatment with 1 gm. of quinine per day, the extension hampering rose, during five days, to 5 6 seconds. After discontinuing the treatment for ten days, the effect of quinine obtained was almost the same as at the beginning of the first treatment. The effectiveness of quinine treatment is therefore reduced by habituation; after a pause it can be resumed.

Quinine Treatment of own Patients.

This writer has used quinine treatment in but few cases and only on patients with severe myotonia

The myotonia in cases of dystrophia myotonica is of minor importance as compared with the dystrophic symptoms; and it is not myotonia but dystrophic symptoms which make about two thirds of the adult patients disabled.

The quinine treatment has been tried, but not continued, in four patients with dystrophia myotonica (Nos. 19, 28, 42, and 105). Two of them noticed no appreciable effect in spite of daily doses of 1.5 gm. of quinine, and although the two others experienced an easing in the hampering of their movements they did not feel inclined to continue the treatment. Only two (Nos 165 and 166) with extremely severe myotonia in the finger flexors wanted to continue the quinine treatment; they were given daily doses of 1 or 1 5 gm. of quinine hydrochloride for one week at a time, with intervals of one week

Myotonia is the dominant symptom in Thomsen's disease, but most of the patients with this disease, nevertheless, know how to reduce the hampering of their movements by keeping in constant activity, and in none of the cases has the myotonia been found so hampering as to render the patient unable to shift for himself Two of these patients with very severe general myotonia tried quinine treatment, but did not wish to continue, although the treatment had a beneficient effect (Nos 10 and 34). Two other patients during a long time have been, for periods of one week, treated with 1.5 to 1 75 gm of quinine per day, with intervals of approximately one week, and they cannot do without this treatment. They administer the quinine themselves according to need (Nos. 28 and 30). Even when they take large doses the hampering of their movements does not, however, completely disappear, but is considerably reduced.

After a few days of these heavy doses, some patients may experience ear-buzzing and a certain degree of deafness, but this is only noticed in remarkably few cases. One patient, after having received a fairly constant quinine treatment for years, felt precordial pains, but an examination of the heart, including electrocardiographical tests, revealed no abnormalities.

Dr. *Hermann*, in the Neurological Department of the Rigshospital,

Copenhagen, investigated the effects of the habituation in quinine treatment in one of my patients (No 34).

The patient was at first treated with 90 cg of quinine sulphate per day by mouth, but without effect He was then given daily doses of quinine hydrochloride 58, 75, 100, 125, 150, and 150 cg with but slight effect on the myotonia

Local injections once a day with 10 cc of quinine hydrochloride solution (1:30) in various muscle groups gave a satisfactory result, as the injected muscle groups were for several days free from myotonia Simultaneously, daily doses by mouth of 50 to 125 cg of quinine hydrochloride were given, in spite of which those muscles, which had not received local treatment, displayed clear myotonic symptoms After four days of this treatment, the patient continued on 100 cg of quinine hydrochloride; after the lapse of four days he was for three days given daily doses of 75 cg of quinine hydrochloride plus 6 gm of calcium gluconate During these seven days the myotonia had decreased to a considerable degree The ailment then grew worse again despite increasing daily doses of quinine hydrochloride and 6 gm of calcium gluconate A few days later the treatment was stopped, as it was evident that the patient had become so habituated that the quinine was without effect

After an interval of five days, treatment was attempted with quinidine sulphate, 30 cg per day increasing over a period of nine days to 80 cg per day, but no noticeable effect on the myotonia was obtained — nor after the administration of 30 cg of quinidine sulphate plus 75 cg of quinine hydrochloride a day for nine days

Taken as a whole, the quinine effect on this patient was comparatively slight, and he clearly presented habituation The administration of calcium gluconate must have had an accentuating action on the quinine effect, as the myotonia was made to disappear as a result of daily quinine doses of 75 cg

The local effect of quinine after injection in the myotonic muscles of quinine hydrochloride solution (1 30) was, in most of the cases recorded electromyographically, investigated by *Buchthal & Clemmesen*. Following injections of 10 cc., the mechanical myotonia as well as the myotonia after voluntary innervation disappeared from the muscle groups thus injected, and the electrical activity, characteristic of myotonia, was untraceable The voluntary muscle contractions and the accompanying electrical activity, on the other hand, was unchanged This local quinine effect completely corresponds to the effect obtained by one half per cent novocaine solution, and — as is explained in the chapter on Electromyography — the opinion is that quinine, like novocaine, by application locally, paralyses the abnormal ability of repetition in the muscular part of the motor end-plate — a quality which is characteristic of myotonia As general quinine treatment can likewise eliminate myotonia in non-injected muscles, it must be supposed that the effect of this treatment is of the same nature as the local quinine effect

Summary

The myotonia may temporarily disappear, in part or wholly, follow-

3.4 to 1.6 seconds, but despite repeated treatment with 1 gm. of quinine per day, the extension hampering rose, during five days, to 5 6 seconds. After discontinuing the treatment for ten days, the effect of quinine obtained was almost the same as at the beginning of the first treatment The effectiveness of quinine treatment is therefore reduced by habituation; after a pause it can be resumed.

Quinine Treatment of own Patients.

This writer has used quinine treatment in but few cases and only on patients with severe myotonia.

The myotonia in cases of dystrophia myotonica is of minor importance as compared with the dystrophic symptoms; and it is not myotonia but dystrophic symptoms which make about two thirds of the adult patients disabled.

The quinine treatment has been tried, but not continued, in four patients with dystrophia myotonica (Nos. 19, 28, 42, and 105). Two of them noticed no appreciable effect in spite of daily doses of 1.5 gm. of quinine, and although the two others experienced an easing in the hampering of their movements they did not feel inclined to continue the treatment. Only two (Nos 165 and 166) with extremely severe myotonia in the finger flexors wanted to continue the quinine treatment; they were given daily doses of 1 or 1.5 gm of quinine hydrochloride for one week at a time, with intervals of one week.

Myotonia is the dominant symptom in Thomsen's disease, but most of the patients with this disease, nevertheless, know how to reduce the hampering of their movements by keeping in constant activity, and in none of the cases has the myotonia been found so hampering as to render the patient unable to shift for himself. Two of these patients with very severe general myotonia tried quinine treatment, but did not wish to continue, although the treatment had a beneficient effect (Nos. 10 and 34). Two other patients during a long time have been, for periods of one week, treated with 1.5 to 1 75 gm. of quinine per day, with intervals of approximately one week, and they cannot do without this treatment. They administer the quinine themselves according to need (Nos. 28 and 30). Even when they take large doses the hampering of their movements does not, however, completely disappear, but is considerably reduced.

After a few days of these heavy doses, some patients may experience ear-buzzing and a certain degree of deafness, but this is only noticed in remarkably few cases. One patient, after having received a fairly constant quinine treatment for years, felt precordial pains, but an examination of the heart, including electrocardiographical tests, revealed no abnormalities.

Dr *Hermann*, in the Neurological Department of the Rigshospital,

CHAPTER III

THOMSEN'S DISEASE

(Myotonia congenita).

A HISTORY

When, in 1876, Dr. Thomsen published his treatise on myotonia, he was sixty-one years old. His manuscript had been ready for several years before he found a cause to make it generally known.

The title of *Thomsen's* work: "Tonische Krampfe in willkürlich beweglichen Muskeln infolge von ererbter psychischer Disposition (Ataxia muscularis)" is, as far as the first part is concerned, due to a suggestion from Professor *Bartels*, of Kiel, whereas the words in the parenthesis (Ataxia muscularis) was Thomsen's own designation for the peculiar, heritable functional disturbance in the muscles.

In Thomsen's opinion, *Bell* had in 1832 described a similar functional disturbance in a patient who experienced a hampering of movements upon psychic impressions. This description is, however, too vague for a recognition of the disease as myotonia.

On the other hand, it is not likely that Thomsen knew *Leyden's* book, "Klinik der Rückenmarkskrankheiten" from 1874, which contains an excellent description of a similar functional muscle disturbance as in Thomsen's cases. *Leyden* observed a strange, familial muscular rigidity in a man of twenty-eight with athletic muscles. A certain exertion of strength was necessary to produce the rigidity, which diminished upon repetition of the movements. *Leyden* did not, however, notice that he had before him a specific syndrome.

Thomsen found that the disease was heritable, as in his own family it could be traced back to 1742. In certain cases it further seemed to be congenital, as he had also ascertained the symptom in several infants. The functional disturbance was localized to all the voluntarily movable muscles, and *Thomsen* thought that the cause must be sought in the central nervous system (C. N. S.) and, most likely, in the brain itself.

ing upon treatment with large doses of quinine (from 1 to 1.75 gm. per day).

There is clear habituation in the use of quinine, rendering the drug ineffective after about eight days' constant administration. Therefore, between each treatment period of eight days, intervals of about eight days must be allowed.

Treatment with large doses of quinine is accompanied by remarkably few inconveniences

Calcium ions in large doses by mouth may accentuate the quinine effect.

Indications for Quinine Treatment.

Patients with Thomsen's disease, whose freedom of movement is hampered to a high degree because of myotonia in the muscles of the lower extremities, may be rendered more able-bodied if their myotonia is reduced by quinine treatment. In such cases, in this writer's opinion, there is indication for a sufficient quinine treatment.

Patients with dystrophia myotonica are frequently disabled by their disease, but not on account of the myotonia. Only cases with slightly developed dystrophic symptoms, but with severe myotonic hampering e g in the use of the hands, will provide grounds for effective quinine treatment.

From my knowledge of patients with myotonic symptoms there are, generally, in these cases no grounds for quinine treatment. In most of them the myotonic symptoms are of so slight inconvenience that they pay them no special attention, and many patients with comparatively severe myotonia, e.g. in Thomsen's disease, are accustomed to them to such a degree that they have no wish for quinine treatment, which will cause them a certain amount of trouble and, at times, inconvenience.

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Several of the affected members of his family suffered from psychosis, and so it was but a short step to connect the mental disorder with the disturbances in the muscular function.

After, and caused by, *Thomsen's* work now appeared a number of casuistic reports, of which mention must be made of *Strümpell's* of 1881 and *Westphal's* of 1883. *Strümpell* termed the syndrome "myotonia congenita", and *Westphal* suggested the designation of "Thomsen's disease". Immediately these names caught on and were attached to the syndrome by *Wilhelm Erb* (1886) in his classic monograph: "Die Thomsen'sche Krankheit (Myotonia congenita)". He here gave an exhaustive clinical description, supplemented by histological muscle examinations — and this was the work that made Thomsen's disease known.

After *Erb's* monograph no greater work appeared until *Nissen's* report in 1923 *Nissen* was a grand nephew of *Thomsen's*, but did not himself suffer from the disease as was the case with several of his brothers and sisters; he therefore knew the disease at the closest of quarters. *Nissen* especially dealt with heredity and with the psychoses so strongly stressed by Thomsen. He demonstrated that the psychoses were independent of the muscular diseases and emphasized that many persons with Thomsen's disease were of high intelligence and had good positions. His clinical description was, however, not quite sufficient, and, in particular, he did not take enough interest in the difference between dystrophia myotonica and Thomsen's disease. *Maas & Paterson* (1939) thought that no significance could be attached to *Nissen's* clinical examinations, and they advanced the theory that Thomsen's disease, paramyotonia, and dystrophia myotonica are identical syndromes.

Among the casuistic reports from the years after *Thomsen's* first treatise, a couple of Danish works must be mentioned. The first was written in 1884 by *Knud Pontoppidan*, followed by *A. Friis* in 1891. Otherwise there is but one Danish report on Thomsen's disease, written by *P. Levison* (1923)

As the years passed there appeared descriptions of diseases with myotonia, which did not quite correspond to the recognized description. In 1886 *Eulenburg* described a disease which in cold temperatures presented a special disturbance in the muscular function which he called paramyotonia. A special chapter will treat of this syndrome, but it would appear that it is only a variant of Thomsen's disease.

During the end of the nineteenth century several descriptions of Thomsen's disease accompanied by muscular atrophy were published, and in 1909 *Batten & Gibb* and *Steinert* described the nosology of "dystrophic myotonia." These reports were further elaborated by *Curschmann* (1912), and it has later become evident that this particular disease

with myotonia is by far the most frequent in occurrence and serious in consequence for the patients in virtue of its dystrophic symptoms.

Talma's description, in 1892, of myotonia acquisita caused a number of reports on acquired myotonia Myotonia acquisita was later described by *Krabbe* in 1934, but it has gradually been agreed that there is hardly any acquired myotonia in existence.

The present writer has for his designation of the classical, heritable myotonia without dystrophic symptoms chosen *Erb's* "Thomsen's disease", because it is easier of distinction from dystrophia myotonica than myotonia congenita

B SYMPTOMATOLOGY

Leyden's and *Thomsen's* descriptions of the symptomatology in Thomsen's disease were further elaborated by *Erb* in 1886, in his well-known monograph on the occasion of the 500 years jubilee of the Heidelberg University This description was so exhaustive that later authors have found little to add

Later years have seen a number of casuistic reports on Thomsen's disease, but new aspects of its symptomatology had not been reached until recent special investigations in myotonia were embarked upon *Nissen's* report of 1923 was first and foremost of a heredobiologic nature, and his clinical descriptions were not so thorough He, for example, gave only slight attention to the question of whether there were signs of dystrophies in Thomsen's family *Maas & Paterson* (1939) took a dubious attitude towards the symptomatology so far described, and opined that Thomsen's disease was identical with dystrophia myotonica *Boeters* (1935) found patients with Thomsen's disease and dystrophia myotonica mixed in the same families, but his clinical investigations are unacceptable, as he described patients unquestionably suffering from dystrophies as having Thomsen's disease

Thomsen's disease is a muscular disease, characterized by more or less widespread myotonia and more or less pronounced muscular hypertrophy The writer's investigations of the symptomatology reveal that there is an essential difference between Thomsen's disease and dystrophia myotonica in that in Thomsen's disease there is found none of the dystrophic symptoms so characteristic of dystrophia myotonica.

In this connexion attention will be given to the social conditions, which in a convincing manner add to the symptomatology when the question is of the difference between dystrophia myotonica and Thomsen's disease.

In the upper extremities, especially the deltoid and upper-arm muscles were hypertrophic, and this was to a lesser degree the case in the muscles of the forearms and hands.

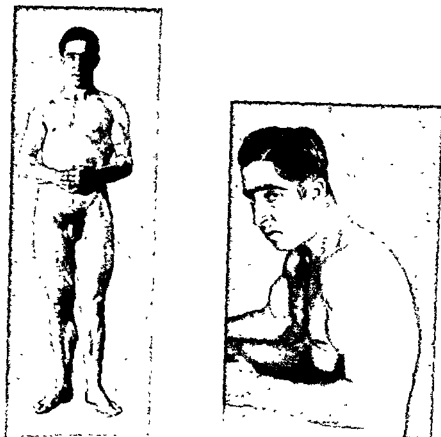


Fig 4

Thomsen's disease (Patient No 10 — Dr Thomsen's family). Very considerable muscle hypertrophy, and universal, extremely severe myotonia

It was frequently found that hypertrophy of the neck muscles resulted in an enlarged girth of the neck. The sternocleidomastoid muscles were as a rule very strong, but in a few patients they were found to be hypertrophic to a smaller degree as compared with the rest of the neck muscles (Fig. 5 and 6)

Most pronounced in the head is the hypertrophy of the mastication muscles Hypertrophy in the facial muscles is, generally, less prominent, but in one patient it was clearly observed (Fig. 6).

Maas & Paterson (1939) advanced the theory that in reality Thomsen's disease is identical with dystrophia and they supported

their view by the observation that the majority of reported cases with Thomsen's disease were of young men whose muscles might become dystrophic in later life.

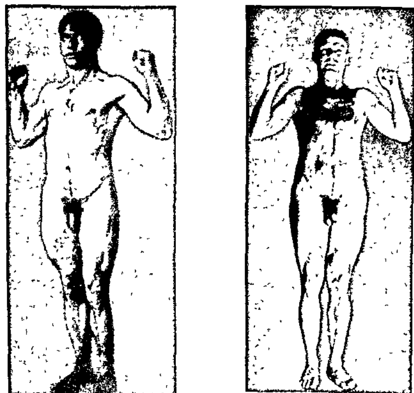


Fig 5

Thomsen's disease (Patient No 28) Photographs taken in 1922 and 1943 During these nineteen years there has been no development of muscle dystrophy Muscle hypertrophy almost unchanged

In one of the writer's cases there is in existence a photograph of the patient in 1922, and a comparison with a photograph of 1943 reveals that no definite change of the development of the patient's muscles has taken place in the interval (Fig 5) At any rate, no dystrophia was found to be present In the older patients, of the Thomsen as well as of the other four families investigated, the muscles were well-developed and there were no signs of muscular dystrophy

It must be emphasized that in the five families with Thomsen's disease examined by me, there was not a single case of muscular dystrophy, and particularly not in patients with myotonia

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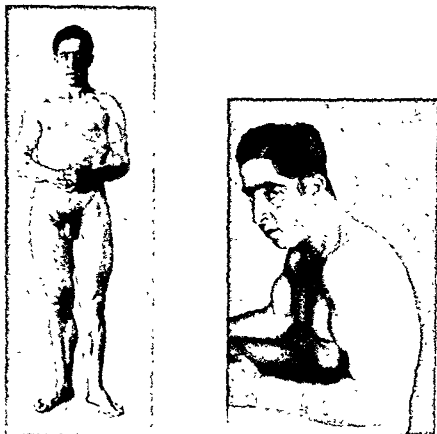


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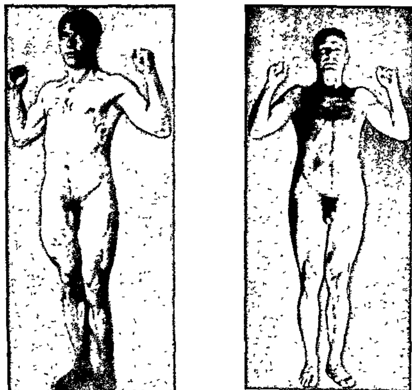


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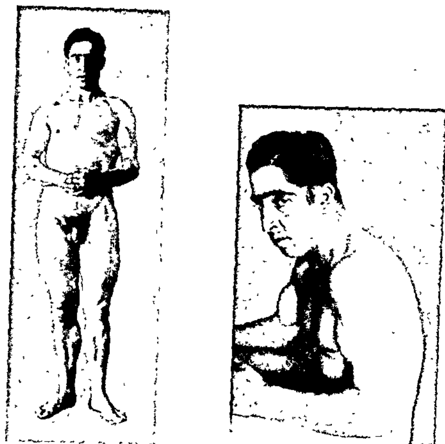


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they were found to be normal, and the reflexes were without myotonic after-effect. The abdominal reflexes, on the contrary, were often accompanied by myotonic protraction.

(3) *Types of Physique.*

A few authors have stressed that patients with Thomsen's disease are robust and of the pyknic type The intention of these statements has been to classify the disease in contrast to dystrophia myotonica, where most of the patients are slim and of the asthenic type.

The writer's material does not allow of so categorical a statement, as some of his patients with Thomsen's disease were of slight build although their muscles were strongly developed

(4) *Non-muscular Symptoms*

Some of the patients with Thomsen's disease were examined more thoroughly, and the results of these examinations may be thus summed up apart from the above-mentioned muscular symptoms it is not possible to demonstrate any abnormalities in patients with Thomsen's disease — a result which is in complete accordance with what others have written on the subject.

(a) *Eyes.*

The sight was normal in all patients, and at the examinations of the families the writer found only one case with senile cataract — in an old woman, who was otherwise well (paternal aunt of patient No. 30). Nor has it been possible to trace any information of cataract in any of the dead members of the families

Eight of my patients were subjected to slit lamp examination In four of them there were found no lenticular opacities (Nos 27, 28, 30, and 34) These patients were from nineteen to fifty-six years of age (average age thirty-eight) In the remaining four (Nos 8, 10, 17, and 29) there were few, small and uncharacteristic opacities

One woman of thirty-four had a slight star-shaped opacity in the posterior cortex and a few white points in the centres of the lenses A male of twenty-three had a thin, filmy, posterior, capsular opacity with radial stronger streaks A male of nineteen had a few small flat opacities in the cortex, mainly located peripherally, and a slight blur of the posterior cortex A male of thirty-nine had a few scattered greyish grains without characteristic position or appearance

However, these lenticular opacities are too slight and uncharacteristic to be considered as clearly pathological signs, and they do not resemble those opacities found in most of the patients with dystrophia myotonica.



Fig 6

Thomsen's disease (Patient No 27) Hypertrophy of facial muscles

(a) *Strength of Muscles.*

The strength of the muscles might be expected to be proportional to the volume of the muscles, but this was not the case.

In cases of severe myotonia the strength was especially reduced in the first movements, which were hampered by myotonia in the antagonists Although the movements became freer, the strength rarely exceeded that of muscles of normal development; frequently the strength did not reach that level

(b) *Consistency and Tone of Muscles.*

When completely relaxed the large muscles in patients with *Thomsen's* disease are of normal consistency, but in cases of extremely severe myotonia the muscles are most frequently felt to be more or less tense, at the same time displaying increased consistency.

The same observations can be made by the usual tone test. Normally, no increase of tone is found at passive movements of myotonic muscles, but in more severe cases a moderate resistance may be caused against the movements because of the myotonia.

(c) *Reflexes.*

Tendon reflexes in several of the examined cases were somewhat weakened, especially in those with severe active myotonia Otherwise

that the disease is discovered when they are called up for military service It is my experience that myotonia in Thomsen's disease is, generally, most severe in male patients where it is therefore more difficult to conceal.

Excluding the propositi, the relation between male and female patients in the written material mentioned is 158 to 139, or 53 per cent men $\pm$ 2.9 per cent.

In Thomsen's family the relation (including this writer's patients), after deduction of 1 proposita, is 30 to 33, or 47 per cent men $\pm$ 6 3 per cent In the other families there are 8 men and 3 women, 4 of the men are propositi, and so the relation is 4 to 3. As will be observed, the relation between the figures of the two sexes is very near 1 to 1.

(2) *Age of Manifestation.*

Of the 152 propositi in the table the great majority had felt the first symptoms already in early childhood Only 17 stated that the disease had set in after the age of twelve, and 5 of these after the age of twenty.

In 22 of my 29 living patients, Thomsen's disease became manifest in early childhood and in some of them already at the age of one year. In the others it became manifest between the ages of ten and twenty.

In the majority of cases the myotonic symptoms set in in early childhood, and it must be reckoned that the statements on the part of the patients as to the manifestation of the disease are comparatively exact. In Thomsen's disease the patients are mentally normal persons, and more credence must be given to their information than to that of patients with dystrophia myotonica

The ages of the propositi in Table 1 go from two and a half to sixty-eight years, but the great majority consists of young men between twenty and twenty-five It must therefore be reckoned that possibly some of them may have had incipient dystrophia myotonica

In the writer's limited material of 29 living patients the average age is 26 4 years. 6 of the 19 patients in Thomsen's family were under fifteen, the others being adults.

It must be noticed as an extraordinary feature that none of my twenty-nine living patients need public relief, nor did any of the deceased receive such aid. The young man, previously mentioned, with very severe myotonia, might need some assistance, but he has not yet applied for it. One of the other patients receives grants towards the quinine treatment and thereby manages to support himself, his wife and one child.

Investigations of the families reveal no social deterioration resulting from Thomsen's disease. In one branch of Thomsen's family without Thomsen's disease, social deterioration has been observed during the life of one healthy family father.

The miserable social conditions characteristic of patients with dystrophia myotonica were not found among the families with Thomsen's disease investigated in Denmark by the present writer.

D. OCCURRENCE AND FREQUENCY OF THE DISEASE

Thomsen's disease has been described in most European countries and in the U.S.A. It is, moreover, known in Japan [(*Kumagai* (1913) and *Mikamo & Hisayoshi* (1930)], but appears otherwise not to have been reported among coloured peoples.

Thomsen's disease must be considered as comparatively rare. Since 1909 the diagnosis "dystrophia myotonica" has been by far the most frequent in reports of diseases with myotonia, and it is possible that before 1909 some of the cases reported as Thomsen's disease have, in reality, been dystrophia myotonica.

I have critically examined the comprehensive casuistic material available in order to ensure, as far as possible, that only clear reports of cases with Thomsen's disease have been included. The material has been collected in Table 1 with special view to the question of heredity; it comprises 265 men and 114 women, besides 16 persons of unspecified sex, totalling 395 patients. This figure does not include the 43 cases from Thomsen's family, described by *Nissen* (1923), nor my 32 cases Were they included the total would be 470 patients (*Boeters*' uncertain cases are not included) There are in all 157 propositi, including my 5.

(1) *Sex.*

Hitherto Thomsen's disease has been found in 303 men and 151 women. Of the 157 propositi, 145 are men and 12 women. Almost all the propositi are males, and this is, no doubt, due to the fact that men to a higher degree than women are hampered in their work by myotonia, and

Table 1.

Author			Propositus	Age	Age at Manifestation	Sick Family Members								
						Parents		Siblings			Others			
						m	f	m	f	u	m	f	u	
Leyden, E.	1874		m	28	e c	—	—	1	—	—				
Seeligmuller, A	1876	(1)	m	22	e. c				1					
—	1878		f	22	e c	—	1	—						
Bernhardt, M	1879		m	22	e. c.	—	—	—	—	—				
Peters	1879		m	20	e c	—	—	—	—	—	—	—	—	
Petrone	1881		m	15	e c	—	—	—	—	—	—	—	—	
Strumpell	1881		m.	36	e. c	—	—	1	1	—	—	—	—	
Ballet & Marie	1883		m.	20	e c	—		—						
Weichmann, W	1883	(2)	m	22	e c	—	—	—	—	—	—	—	—	
Westphal	1883	(2)	m.	20	e. c.				1					
Pontoppidan, K	1884	(1)	m.	17	e c			—	1	—				
—	1884	(2)	m.	24	e c	1		1	2		2			
Rieder	1884		m.	26	e c									
Vigouroux, R	1884		m.	19	e c	—	—	—						
Bernhardt, M	1885		m.	16	e c.	—	—		1		1	1	2	parents related
Eulenburg, A & Melchert	1885		m.	22	7.	—	—	2	1		—	—	—	
Pitres, A & Dallidet	1885		m	25	e c.		1	1	1	—				
Erb, W	1886		m	21	16.	—	—			—				
—	1886		m	15	e c.	—	—	1	—					
Fischer, G	1886		m	21	16									
Banham, F	1887		m	18	12									
Buzzard, T	1887		m	20	e c	—	—	1		—				
Jacoby, G W.	1887		m	24	e c									
Uebeleisen	1887		m	20	e c	—	—	1	2	—	1			paternal grandfa
Blumenau	1888		m	30	e. c			1						
Danillo	1889		m	24	e c							1		
Erb, W	1889		m	?	?					4				
—	1889		m	?	?									
White, W H	1889		m	19	9	1	—	—	1		2			
Wising, P J	1889		m	19	e c					—	—	—	—	
Cook, A & Sweeten, B	1890		m	19	e c	1		—	1	—	1	—	—	
Deleage, F	1890		m	37	e c				1					
Dreschfeld	1890		m	14	e c	—	—	2			1			
Grenier, P	1890		m	34	e c		—			—		—		
Herschell, P	1890		m	28	e c			1		1				
Jolly	1890		m	20	e c									
Nearonoff, V N	1890		m	23	e c	1								dominant through 4 generations
Renner	1890		m	20	e c		1				1	1	—	
—	1890		m	17	e c.	1					1			dominant through 3 generations
Angell, E B	1891		m	21	e c	—	—	1			—	—	—	
Friis, A	1891		m	10	e c	1		1						
Seifert, P	1891		m	25	e c	—	—	1	—					
Hollmann, O	1894		m	14	6	1					3	4		
Nonne	1894		m	8	e c									
Susskand, A	1894		m	20	16		—		—		—	—	—	
Dejerine, J & Sottas, J	1895		m	32	e c									
Niedendarp, T	1895		m	30	e c	—	—	—	—	—				
Moltschanoff	1896		m	33	12									
Bechterew, W v	1897		m	46	e c									
Nikonoff, S	1897		m	33	e c	—	—	—	—	—	—	—	—	1 child —
Wersiloff, N M	1897		m	23	10	—	—	—	—	—	—	—	—	
Wichmann	1897		m	39	e c	—	—	—						
Alsberg, G	1898		m	23	e c	—		—						
Jacoby, G W	1898		m	28	18		—	—	—	—				

Author	Year	Propositus	Age	Age at Manifestation	Sick Family Members: Parents		Siblings			Others			
					m	f	m	f	u	m	f	u.	
—	1898	m	34	28		—	—	—					
Kron, H	1898	m	17	10									
—	1898	m	27	15.				1					
Preston, G J	1898	m	21	e c		1							
Gessler, H	1899	m	20	e c									
Koster	1899	f	18	12			1	1					
Salomonsen, J K A W	1899	m	20	e c									
Beck, R	1900	m	24	e c	—	—			—				parents related
Jones, J T	1900	m	25	e c.	—	—	1	—					
Mahler, J & Beck, R	1900	m	24	e c	—	—	—	—	—	—	—	—	
Gardiner, C F	1901	m	6	e c		1							
Koch, J	1901	m	21	e c									
Bauer, M	1902	m	26		—		—						
Braun, W	1902	m	23	e c			2						
—	1902	m	23	5		—	—						
—	1902	m	21	e c	—	—			—				
Brinckmann, J J	1902	f	12	e c	—	—		1		1			
Luce	1902	m	28	?	1					1			
Pånski	1902	m	27	e c						1	1		paternal grandfather 2 children +
Rosenthal, M	1903	m	29	25	1	—	3	—					
Carneross, H	1903	m	22	e c									
Jaquet, A	1904	m	26	e c	1								
Anderson	1904	m	21	14		1	1	1					
Koch, H	1905	m	22	e c	—	—	—	1	—	—	—	—	
Dreschfeld, J	1905	m	16	e c		1	1	1		1			
Meara, F S	1906	m	10	2	—	—	—	—	—				
Beyer	1906	m	22	e c						1	—	—	
Meeus, F	1907	m	19	e c	—	—							
Atwood, C E	1907	m	23	e c	—	—	1	1		—	—	—	
te Kamp	1907	m	20	e c		1		1		8	5		mother's parents both myotonia dominant inheritance in both families
Mann, L	1907	f	10	e c									
Pelz	1907	m	33	e c		1	1				1		dominant through 3 generations
Birt, A	1908	m	68	e c									dominant
Brissaud Bauer & Gy	1909	m	16	e c									
Bartelt, Robert	1910	m	21	e c				2					
Sedgwick, J P	1910	m	59	e c	1		1	1		5	5		dominant through 5 generations
Allaire & Denès	1911	m	22	?									familial
Hirsch, C	1911	m	22	e c									
Kliensberger	1911	m	19	e c			—	—	—	—	—	—	
Pesme	1911	m	21	e c									familial
Dejerine	1912	m	44	40						—	—	—	
Ortleb, W	1912	m	23	12						—	—	—	
Schmidt, O	1912	m	16	e c	1						2	—	dominant through several generations
Boot, G W	1913	m	21	e c		1			1				
Gildesmeister, M	1913	m	24	?									
Numagai	1913 (1)	m	23	19		1	—						parents half-siblings
Skutetsky, H	1913	m	23	4			—						
Collier, J	1914	f	11	9				1		—	—	—	
Goldenberg, B	1914 (1)	m	16	e c	—	—							
—	1914 (3)	m	24	12			—	—					
Hertz, A F	1914	m	25	8	—	—	2	1					
Rosenblom, J & Cohoe, B A	1914	m	22	12						1	—	—	twin brother and sister with myotonia paternal grandfather +, father died at early age

Author			Propositus	Age	Age at Manifestation	Sick Family Members: Parents m	Parents f	Siblings m	Siblings f	Siblings u.	Others m	Others f	Others u	
Jones, W A	1915		f.	41	e. c.	—	1	—	—					
Michaud	1915		m	23	e c									
Lortat, Jacob & Sezary, A	1916		m	22	e. c.			—	1		1			
Scharptf	1916		m.	19	e c	—	—	—	—	—				
Severin	1916		m	21	17.			1	—					
Taylor	1916		m	24	10									
Thomson, J.	1916		m.	6	e. c	—	—				—	—	—	
Toomey, N.	1916		m	44	14						3		4	4 children +
Uebe, E.	1916		m	23	12.					—				
Lewandowsky, M.	1917		m	40	e. c.								—	3 children —
Ochss, H E	1917		f	6	3½	—	—	—	1					
Erlach, H. v.	1918		m.	32	e c.	—	—	1	2		—	—	—	
Jellinek	1918		m	41	?									
Pappenheim, M. & Bittner	1918		m	23	e c				1					
Morrison, M M	1920		m.	34	10.		1							
Winkelman	1921	(1)	m	12	e. c.									dominant throu
Rosett, J	1922		f	13	e c.		1	1	2		3	1		3 generations
Roth, C	1922		m	18	e c	—	—	—	—	—	—	—	—	
Stiefler, G.	1922		m	13	e. c.		—						—	
Bürger, Max & Schellong, F	1923	(2)	m	42	?	—	—	2			3			3 sons +
Stattmuller	1923		m	15	15		1	1			2	4		dominant heredit
Voisin, R	1923		f	13	?	1							4	dominant throu 3 generations
Yealland, L R.	1923		m	18	e c									
Majerus	1924		f	12	6.	—	—	1						
Barker, L. F.	1930		f	43	10			—	1		1			
Monrad-Krohn, G H	1930		m	27	17									
Pamboukis, G	1930		m.	17	4.									
Wassermeyer, H & Dutte, K	1930		m	26	23									
Ruhemann, K	1932		m	31	19						—	—	—	
Friesz, J & Mohos, E	1933		m.	20	11		—							
Jelliffe, S. E & Ziegler, L	1933		m	28	e c	—	1	1	1	—	—	—	—	
Kramer, F. & Quadfasel, F	1933		m	54	21.									
—	1933		m	54	40									
Comroe, B I	1935		m.	19	e c	1			1		1	—	—	dominant throu
Knaur, E A	1936		m.	15	12.	1	1		1		12	8		3 generations
Lindsley, D B. & Curnen, E C	1936		m	18	e c			—	—					
Russel, W R & Stedman, E.	1936		m	21	?			4						
Smith, W A	1937		m	19	e. c				2					
Breitfort, K	1938		m.	9	3-4.	—	—			—	—	—	—	mother —, mate
Eichler, W & v Hattingberg	1938		m	12	e c			1			1			grandfather +
Hawke, W A	1938		m	7	2	—	—	—	—	—	—	—	—	brother —
Lonergan, R. B & Paskind, H A.	1939		m.	14	3-4									
Wenckert, A	1938		m.	62	e. c			1		—			—	children —
Hermann, R W	1939		m	61	e c	1			1			3		dominant through 4 generations
Kiehl, W.	1939	(1)	m	2½	5 w.	1			1		1			dominant through 3 generations
Klein, C	1939		f	37	7.		—	1						
Liebenam, Leonore	1940		f.	46				—	3	—				enzygotic twins with myotonia
Biemond, A.	1943		m	34	e. c	1		1	1		3	1		dominant

e. c. = early childhood

m. = male.

f = female.

u = unknown sex.

w = week(s).

E. HEREDITY

Already *Leyden* showed that what was probably Thomsen's diseas[e] might occur familially, as the brother of his patient also suffered fro[m] the disease.

In 1876 *Thomsen* in his own family was able to follow the disease continually through five generations back to a woman, who was born in 1742 In 1923, and later in 1934, *Nissen* supplemented the pedigree of this family and was now able to trace the disease through seven generations. *Nissen* was unable to follow two branches of Thomsen's family, because they lived in Denmark, but the present writer has investigated one of these branches and is able to confirm *Thomsen's* and *Nissen's* descriptions of the dominant heredity Of dead or living members of the family with the disease 64 are now known.

Most works on these subjects, and especially most text-books, cite Thomsen's family as a proof that the disease is dominantly hereditary. Other authors are more careful and confine themselves to stating that it is familial [*Stein* (1934)], or heritable [*Lenz* (1927)]. *Vejnarova* (1930) thought that its heredity was dominant as well as recessive.

Almost all hitherto published reports on the heredity of Thomsen's disease have been based on investigations of one or a couple of families

In Table 1 the writer has given the hereditary relationship of 152 propositi cited by other authors.

In 68 cases there was either no information on heredity, or it was merely reported that no similar case had occured in the family Such information must, however, be taken with all reserve, as only very few authors have made any regular investigation of the families

In 40 cases Thomsen's disease had been demonstrated in parents and children, and in 12 cases in three or more consecutive generations [*Renner* (1890), *te Kamp* (1907), *A. Pelz* (1907), *Sedgwick* (1910), *O Schmidt* (1912), *Rosett* (1922), *Stattmuller* (1923), *Voisin* (1923), *Knauer* (1936), *Kiehl* (1939), *Hermann* (1939), and *Biemond* (1943)] This means that in more than one quarter of the families described the disease was dominantly hereditary

In 42 cases the disease was not observed in the parents, but in other relatives, as siblings, cousins, uncles etc In 2 cases it was only reported that the disease was familial. In 23 cases the parents had not been examined, and in 1 case the mother only Of the remaining 16 cases it was stated that the parents were free from Thomsen's disease, but it is not always possible to see whether the authors in question have made investigations in this respect or satisfied themselves with the statements of the propositi. In 12 of these 16 families the disease was only discovered in brothers and sisters [*Leyden* (1874), *Strumpell* (1881), *Eulenburg* &

Melchert (1885), *Erb* (1886), *Buzzard* (1887), *Dreschfeld* (1890), *Angell* (1891), *Jones* (1900), *Koch* (1904), *Atwood* (1907), *Hertz* (1914), and *Majerus* (1924)], but there is no information of consanguinity between the parents. It has, unfortunately, proved impossible to obtain *Vejnarova's* report of 1930 with his supposition of the possibility of recessive heredity. Only a brief summary has been accessible, and the reason for his supposition is therefore not known.

It appears from the table that in more than 25 per cent of the cases there was a probability of dominant heredity. In well over another 25 per cent there were signs to indicate that the disease was heritable, and in more than half of the latter group dominant heredity could not be excluded as a possibility. In only 8 per cent there was the possibility of recessive heredity, but the information concerning the parents was unsatisfactory, and there was no description of consanguinity in these families. The possibility of recessive heredity is therefore comparatively slight.

In *te Kamp's* family both parents had Thomsen's disease with dominant heredity in the families of both parents. There were nine children, five of them stillborn. Three daughters had Thomsen's disease as was the case with their children, but one daughter and her two children were sound. The high number of stillbirths might indicate that the homozygotes were less capable of surviving than the heterozygotes. One of the daughters and her children were free from Thomsen's disease, and this fact corresponds well with the theory of simple dominance, when it is supposed that the parents were heterozygotes.

There were comparatively many female patients in *te Kamp's* family, and he thought that heredity through males caused the disease to disappear rapidly from the family, whereas when inherited through females the disease had a greater tendency to continue.

This observation has not been confirmed by other authors. In Thomsen's family the disease was equally frequently inherited through men and women without any qualitative difference, and in *Sedgwick's* family it was inherited through men for three generations; thus, *te Kamp's* observation must without doubt be ascribed to a coincidence.

It appears from the many families observed that the heredity of the disease is not sex-linked.

In a work from 1892 with the title "Nachträgliche Bemerkungen über Myotonia congenita"*, *Thomsen* writes that the heredity may be atavistic He did not state in what branch of the family this had occurred, and there are no such examples in *Nissen's* pedigrees.

* "Further Comments on Myotonia Congenita"

Nor have I been able to establish any atavism in that branch of the family I myself have investigated

There is only a single report on Thomsen's disease in enzygotic twins, both of whom had the disease from early childhood [*Liebenam* (1940)].

Up to now no investigations have been made into the effective fertility of patients with Thomsen's disease, but judging from the many family descriptions there seems to be no question of reduced fertility.

Intensification of the disease from generation to generation has never been noticed. Nor are there reports to indicate that patients with Thomsen's disease should be less long-lived than their relatives

(1) *Own Investigations.*

This writer's material comprises five families in which Thomsen's disease has been found. The first family is one branch of the big family which *Thomsen* and *Nissen* described and belonged to.

My investigations were carried out in 584 persons, 465 of whom are living Thomsen's disease was found in 29 living persons and must supposedly have been present in 5 of the dead.

I do not venture to say that I have found all cases of Thomsen's disease in Denmark Thus it has been impossible to trace descendants of the Danish families with the disease described by *Pontoppidan* (1884) and *Friis* (1891). As most of the afflicted patients can look after themselves and, further, do not want to disclose the disease, it is my opinion that there are more cases in existence than noticed up to the present moment

In Thomsen's family it is incorrect to speak of a propositus in the ordinary sense of the word, but in the other four families my investigations took a propositus as a starting point, these propositi were in two cases provided through hospitals and the other two were traced through the records of the Invalidity Insurance Court.

My investigations and examinations of the families from 1941 to 1943 were rendered difficult by the ever increasing obstacles of travel during the war period. I have, as far as possible, personally visited all the living members of the families, but in some cases I have had to satisfy myself with an examination by the local physician, as regards members of secondary importance, the investigations have in some cases been limited to questionnaires

At these investigations I have examined for myotonia and muscle development I have, further, made it a special point to investigate any symptoms of dystrophia myotonica.

The results of the examinations of the families are found in pedigrees

Melchert (1885), *Erb* (1886), *Buzzard* (1887), *Dreschfeld* (1890), *Angell* (1891), *Jones* (1900), *Koch* (1904), *Atwood* (1907), *Hertz* (1914), and *Majerus* (1924)], but there is no information of consanguinity between the parents. It has, unfortunately, proved impossible to obtain *Vejnarova's* report of 1930 with his supposition of the possibility of recessive heredity. Only a brief summary has been accessible, and the reason for his supposition is therefore not known.

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The results of the examinations of the families are found in pedigrees

of each family. It has been impossible to show any relationship between the five families in my material, which are moreover from widely different parts of the country.

(2) *Analysis of the Pedigrees.*

The results of the investigations are stated separately for each family, as there seems to be some variance between the heredity when comparing the families Moreover the material is too small to allow any statistical genealogical computation beyond an estimate of the probability of inheritance in Thomsen's big family on the part of the children of patients with Thomsen's disease.

To Thomsen's family has been devoted an especially thorough study with genealogical description of the past generations, because my investigations revealed that *Thomsen's* and *Nissen's* pedigrees were not quite complete with regard to the former generations.

The pedigrees directly show that there is no reduced fertility in patients with Thomsen's disease, nor does the viability seem to be affected. Dr. Thomsen and his mother both grew old, and this was also the case with the afflicted members of earlier generations in the branch of the family investigated by me The father of family No. 2 also reached an extremely advanced age.

Intensification of the disease in following generations has not been noticed.

Family No. 1 (Dr. Thomsen's Family).

This family descends from two noble families which in former times immigrated into Denmark from Northern Germany. In the eighteenth century members of these families were Danish officers or high civil servants. Dr. Thomsen's great-grandmother, *Frederikke Christiane Ludovica v Grambow,* is the first person known to have had myotonia The names of her parents were van der Luhe and von Grambow, and by marriage she acquired the name von Barner.

Information of Dr. Thomsen's family can therefore be taken from a genealogical table of the family von Barner, written by the Danish chamberlain *Konrad v. Barner.* This book was published in 1910 by an archivist in Schwerin, Germany.

The information contained in the book mentioned, as regards Frederikke v. Grambow's parents, siblings, and children, is not complete. I have found supplementary particulars by going through "Efterladte Papirer fra den rewentlowske Familiekreds Tidsrum 1770—1827"* vol 7, p 514, edited by *Louis Bobé* (1906).

* "Posthumous Papers of the Rewentlow Family Circle. Period 1770—1827"

Frederikke v. Grambow's father, *Volrad Levin v. Grambow*, died in Elsinore in 1761 a Lieutenant-General in the Danish army; it can, therefore, with all probability be said that he did not suffer from myotonia. Her mother, *Barbara Sophie v. d Luhe*, came of an officer family. She died in 1766, fifty-five years old There is no information of myotonia in her or her brothers, who were Danish officers of high rank.

Frederikke v Grambow had five brothers and sisters, of whom brief mention will be made here as *Thomsen* and *Nissen* have only mentioned two of them

1 *Didrik Otto v Grambow*, died a Danish diocesan Chief Crown Officer at Aggershus, Norway, aged 41 He was married, but there is no information of children
2 *Elisabeth Tugendreich v Grambow* married one v Barner who was a county governor and landowner near Kallundborg, Denmark She died aged 44 and had three children who all died before the age of 11
3 *Charlotte Amalie v Grambow* married the Danish General v Wackenitz and lived in Christiania, Norway She died aged 36, and there is no information about children
4 *Henrikke Juliane Marie v Grambow* was, according to *Thomsen*, free from myotonia, but became psychotic She was unmarried and died aged 63 in a Copenhagen convent
5 *Louise Sophie v Grambow* was also, according to Thomsen, free from myotonia, but became psychotic She died comparatively young, unmarried
6 *Frederikke Christiane Ludovica v Grambow* was born in 1742 Of her *Thomsen* stated that she had slight ("angedeutet") myotonic symptoms She married a major in the Danish army, Nicolaj Caspar Hartvig v Barner, and they had three sons of whom the two first died young After the birth of the third son she died in childbed having puerperal mania, aged 28 This son, *Tugendreich v Barner*, is thus the only descendant of Frederikke v Grambow's parents He had myotonia and could therefore not become an officer He went into the Customs Service and was made customs inspector in Nykobing Mors, Denmark As a consequence of psychosis with mental deterioration he was, however, pensioned off when 40

Tugendreich v Barner had four children, two sons and two daughters who all had myotonia One of these four was Thomsen s mother

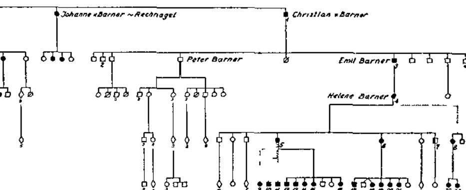
1 *Christian Henrik Julius v Barner* had severe myotonic symptoms He was not particularly well gifted, and he became a customs officer in Copenhagen He had four children *Nissen* (1923) has given an account of his descendants No members of the younger generations had myotonia
2 Thomsen's mother, *Henriette Nicoline v Barner*, was an energetic and intelligent woman with slight myotonic symptoms She married twice and lived in South Slesvig Seven of her thirteen children had myotonia *Thomsen* and later *Nissen*, both descendants of hers, have given detailed accounts of this family
3 *Johanne Konradine Christine v Barner*, had, according to *Thomsen*, severe myotonia, and was poorly gifted She married a subordinate Danish customs officer, Frederik v Recknagel, and lived, *inter alii*, in Ribe and in Ballum, near Tonder, South Jutland She died in 1871, aged 72, had four daughters about whom but scanty information is available Two of them might have had myotonia The Recknagel family showed no interest in these four women who were unable to carry

Dr Thomsen's Family

on the name, and up to the present time I have made vain attempts to trace any of their descendants

4 *Christian Frederik August v Barner*, b 1801, d 1867, was also a subordinate Danish customs officer who lived, *inter alia*, in Skagen and Skive, Jutland *Nissen's* information is that he had lighter myotonic symptoms, but grew insane in his late thirties One gets the impression that socially he was worse off than his father He had thirteen children of whom *Thomsen* reported that some were lunatics and several had myotonia It was impossible for *Nissen* to trace this branch of the family, but I succeeded in finding descendants of two of the thirteen children mentioned

1 *Tugendreich Frederik Carl Barner*, b 1829, d 1884, was a teacher of languages at Skive, Jutland It is not known whether he had myotonia No children
2 *Julius Heinrich Konrad Barner*, b 1831, was a goldsmith, but died in the mental hospital near Aarhus, Jutland It is unknown whether he had myotonia
3 *Eggert* ... emigrated to America and had six ch... tonia
4 *Peter* ... was tradesman, hotel-owner and confectioner, ... ing age He married twice and had eleven children, eight of whom are still living The living descendants do not suffer from Thomsen's disease, and this appears also to have been the case with the father and the dead children The social deterioration can be traced to the descendants, twenty-two of whom are living, they do not present signs of Thomsen's disease, nor dystrophic symptoms



5 *Frederikke Marie Barner*, b 1839, d aged 4 It is unknown whether she had myotonia

6 *Emil Kathinkus Jensenius Barner*, b 1841, d 1888, was manager of a travelling circus The eldest children of Peter Karelius' children (*supra*) recollect him as a very muscular man, and his grandchildren know that he had myotonia He married a gipsy The Barner Genealogical Table states that he had three children According to the grandchildren, two of these three children had been born to his wife before her marriage, and Emil Kathinkus Barner had only one child, a daughter, *Helene Barner*, who had a slight degree of myotonia

7 *Frederik Marius Barner*, b 1844, d c 1924 Unmarried tradesman in the country His nephews and nieces have visited him several times and did not notice myotonia He was very fit and agile

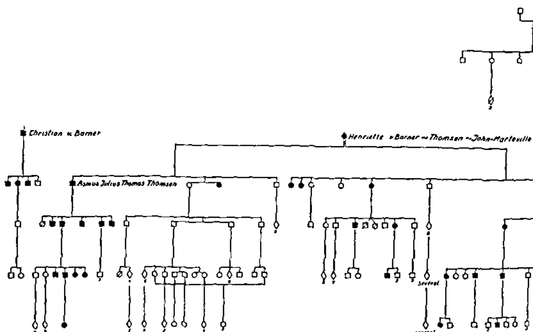
8 *Ditlev Fransiskus Peter Barner*, b 1845, emigrated at an early age to Australia, and the family has had no connexion with him

9 *Olav Barner*, b 1848, d 1880 Emigrated at an early age to Germany, married and had one daughter There is no information about them

10—13 *Four sons*, who died in infancy

Helene Barner, b 1873, d. 1937, had Thomsen's disease to a slight degree. She travelled with a circus and other fair-ground entertainments and had nine children by two husbands All the children are living, and four of them — from both marriages — have Thomsen's disease which is also found in fifteen of the grandchildren

Almost all of Helene Barner's children and grandchildren are "wan-



Dr Thomsen's Family

on the name, and up to the present time I have made vain attempts to trace any of their descendants

4. *Christian Frederik August v Barner*, b 1801, d 1867, was also a subordinate Danish customs officer who lived, *inter alia*, in Skagen and Skive, Jutland *Nissen's* information is that he had lighter myotonic symptoms, but grew insane in his late thirties One gets the impression that socially he was worse off than his father. He had thirteen children of whom *Thomsen* reported that some were lunatics and several had myotonia It was impossible for *Nissen* to trace this branch of the family, but I succeeded in finding descendants of two of the thirteen children mentioned

1 *Tugendreich Frederik Carl Barner*, b. 1829, d 1884, was a teacher of languages at Skive, Jutland It is not known whether he had myotonia No children.
2 *Julius Heinrich Konrad Barner*, b 1831, was a goldsmith, but died in the mental hospital near Aarhus, Jutland It is unknown whether he had myotonia
3 *Eggert Darius Wilhelm Marteville Barner*, b 1834, emigrated to America and had six children It is unknown whether he had myotonia
4 *Peter Karelius Martincus Barner*, b 1837, d 1876, was tradesman, hotel-owner and confectioner, deteriorating socially with his growing age. He married twice and had eleven children, eight of whom are still living The living descendants do not suffer from Thomsen's disease, and this appears also to have been the case with the father and the dead children The social deterioration can be traced to the descendants, twenty-two of whom are living, they do not present signs of Thomsen's disease, nor dystrophic symptoms

(3) *Result of Heredity Investigations.*

While the heredity in Thomsen's family was clearly dominant, this seems not to be the case in the four other families investigated by me. The appearance in families Nos 2 and 4 would indicate dominant heredity with varying manifestation. The cases of families Nos. 3 and 5, where the disease was found in siblings — but not in their parents or their relatives — might indicate recessive heredity, but consanguinity has only been ascertained in the latter family

It appears from investigations by other authors, as well as by this writer, on the heredity of Thomsen's disease, that it is probably always hereditary. The heredity in most cases seems to be dominant, in some cases, however with varying manifestation. Recessive heredity is not likely, but the possibility cannot be excluded.

F. CASE REPORTS

The present investigation covers five families in which cases of Thomsen's disease have been demonstrated My investigations comprise 584 persons, of whom 465 are living Only that part of Dr Thomsen's family living in Denmark has been investigated

Among the living persons the writer found 29 with Thomsen's disease. Five of the dead were reported to have had symptoms indicating Thomsen's disease.

Reports of the sick members of the families are given, and the enumeration corresponds to that of the pedigrees. Considerations of space have necessitated very short descriptions, but the complete case records are to be found in The University Institute for Human Genetics, Copenhagen

Family No 1 (Dr Thomsen's Family).

Mention will here be made only of the part of the family, the living members of which this writer has been able to investigate They are descendants of Thomsen's maternal uncle, Christian Frederik August v Barner, b 1801, d aged 66 He had thirteen children, several of whom, according to Thomsen, were less well gifted or insane, and several had myotonia *Two of these thirteen siblings have descendants in* Denmark

Peter Karelius Martincus Barner, b 1837, d aged 59 He married twice No members of this branch had myotonia

Emil Kathinkus Jensenius Barner, b 1841, d aged 47 He was manager of a travelling circus, and has undoubtedly had Thomsen's disease

His daughter, *Helene Barner*, had Thomsen's disease, and there are in all nineteen patients with the disease among her living descendants

derers", of no fixed abode, marked by their gipsy descent in appearance and mode of living. Only few of them have permanent addresses.

Through *Gudrun Bruun* who with *Erik Bartels* has examined the Danish gipsy families, I succeeded in establishing a personal contact with this family; they have, admittedly, been obliging, but at the same time somewhat more difficult to investigate than the rest of the families examined by this writer

Up to this point Thomsen's vast family comprises about 315 members, 64 of whom have been noted as having Thomsen's disease. A computation of children of parents with Thomsen's disease resulted in 112, 57 being afflicted (in counting Helene Barner's father's siblings, the three who emigrated to America have not been included). This means a probability of contracting the disease of about 50 per cent.

Analysis of the pedigree shows that the disease is inherited continually and that *it is found in several families of half-brothers and -sisters* Further the heredity is not sex-linked.

Thomsen's family thus presents a simple dominant heredity with strong penetration, and regardless of sex.

Family No. 2.

In 1922 the propositus was demonstrated in the Danish Neurological Society by *P. Levison*. In 1941 I succeeded in finding the patient.

The father of the propositus had herculean muscle development and stiffness in the legs for initial movements, he has undoubtedly had Thomsen's disease. Of his fifteen children, four had Thomsen's disease, but among the living eleven children and five grandchildren of these four patients, there is no case of myotonia, but several of muscle hypertrophy.

Family No. 3.

In this family Thomsen's disease was found only in the propositus and a brother of his. In the two sons (*b. 1935* and *1942, respectively*) of these two patients, objective examinations revealed no signs of myotonia, but, in the elder, somewhat doubtful subjective symptoms.

Family No. 4.

Thomsen's disease has been demonstrated *in one of the maternal* aunts of the propositus and is stated to be present in one of his maternal uncles, whom it has been impossible to examine The mother and two sisters of the propositus were healthy.

Family No. 5.

Only the propositus and his slightly older sister had Thomsen's disease. There are no other siblings The parents of the propositus are cousins, children of binovular twins

7

8

Comparatively moderate active myotonia in the mastication muscles, tongue, arms, hands and legs Mechanical myotonia in many muscles Ophthalmoscopy 1942 a very slightly star-shaped opacity in the posterior cortex One or two fine white

9

nexion with pregnancy and birth Has a couple of times been rigid as a statue Myotonia worst in cold and hot temperatures After having kept hands and lower parts of forearms in water of 7 to 8 degrees centigrade for 15 minutes the myotonia eased noticeably Menstruations somewhat irregular

cent

10

general active myotonia Moves about with difficulty Muscles most frequently hard and tense, but he is able to relax General mechanical myotonia Strength quite

11

dystrophy

12 Male, s., unskilled worker, aged 17 Thomsen's disease Myotonia to a comparatively pronounced degree from early childhood Is able to perform his work Mentally completely natural Medium build with strong muscles without the abnormal volume Active and mechanical myotonia in most muscles Difficulty in moving on stairs.

13

myotonia, spread to most muscles

The investigated part of Thomsen's family comprises 106 persons, of whom 73 are living Among the living, 19 have Thomsen's disease, and among the dead there are 3 certain cases Available information concerning the 106 persons reports only one certain case of insanity, in the second generation Among the younger generations, tendency to dromomania is reported in one deceased male, but no living person is insane. There is one case of mental deficiency among the living members, a boy with myotonia, microcephaly, and imbecility, but this patient does not present the typical mental changes, characteristic of dystrophia myotonica

None of the living patients have muscle dystrophy or other dystrophic symptoms, and there are, especially, no cases of manifest cataract

1 Male, m , customs officer, b 1801, d aged 66 *Thomsen's disease.*
According to Thomsen and Nissen he had severe myotonia and deteriorated mentally because of insanity starting in his late thirties Socially he was comparatively badly off

2 [illegible]

3 [illegible]

disease

4 Female, m to a circus manager, d aged 74 *Thomsen's disease*
Myotonia from childhood, but most pronounced between the ages of 14 and 16 Energetic woman with strong muscles Photograph shows strong face without signs of muscle dystrophy No visual disturbances

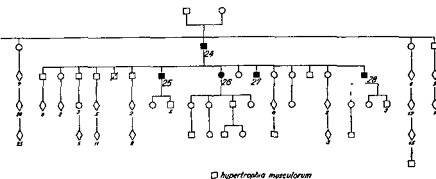
5 Female, m to a swing-owner, aged 46 *Thomsen's disease*
At the age of 7, possibly earlier, the myotonia was manifest Worst between ages of 10 to 17, since then constant Has gradually learnt to suppress the inconveniences with the result that the myotonia is no longer a hindrance. Feels myotonia at its worst in *cold temperatures and when fatigued*
Despite her myotonia she was an aerial acrobat in her youth Before every performance she had to stand behind the curtain of the arena, making energetic movements with arms and legs Her well-developed muscles gave the audience the impression that she was very strong She still lives the life of the travelling caravan as did her grandmother, who was a gipsy, Menstruation and libido completely [illegible]

6 [illegible]

Among those living, three have Thomsen's disease, and among the dead there was one with presumably Thomsen's disease and one with Thomsen's disease It has been impossible to demonstrate dystrophic changes, especially are there no cases of cataract One young man, living in the U S A, is, after puberty, disintegrating mentally, but it is impossible, from his family's description, to form an idea of the nature of his disease

Several of the unaffected members of the family are distinguished by being very big and strong of build, and a few have muscle hypertrophy. Myotonia most often, but not solely, appears in big persons but the muscles are always hypertrophic in these cases

The disease of the propositus was recognized by *Ph Levison* in 1922, but the present writer has traced the patient, and through investigations of the family found the other cases here mentioned



24

25

encephalitis

26 Female, m to a baker, aged 59 *Thomsen's disease* From the age of 20 stiffness

other muscles but those of the legs Impossible to demonstrate mechanical myotonia, which in the legs is obscured by a rather considerable degree of adiposity No visible cataract

27

from myotonia for a period of 8 days

Is a bachelor, somewhat eccentric with own ideas about food and mode of life Intelligence appears to be normal He is friendly and helpful, and normally balanced Is small and of slight build Hypertrophic muscles all over the body make

14. Girl, daughter of a swing-owner, aged 14 *Thomsen's disease.* Myotonia from early
oes well
tive and

15

mal, no
various

16. Girl, daughter of a swing-owner, aged 8 *Thomsen's disease.*
Myotonia from age of 4 Quick and intelligent. *Mentally natural. No muscle hypertrophy, but very* pronounced myotonia in most muscles No dystrophy.

17 *Male, s, unskilled workman, aged 19 Thomsen's disease. Myotonia* in almost all muscles as long as he can remember *Myotonia aggravated at age of 13 Inconvenienced by myotonia* in his work ... with his hands. Is, nevertheless, able
Is somewhat quiet and re ... big muscles, general appearance he ... leido-mastoid muscle a little thinner ... y big

rior cortex (s l e)

18

myotonia of medium magnitude No muscle dystrophy.

19 Female, s, domestic servant, aged 16 *Thomsen's disease* Universal myotonia and big muscles from early childhood Able to perform her work. *Mentally normal* All muscles *strong* Universal active and mechanical myotonia. No *muscle dystrophy.*

20. Girl, daughter of a butcher's assistant, aged *12. Thomsen's disease. Myotonia from* age 3 or 4 Is *inconvenienced* when running and especially when doing *gymnastics* Mentally normal *Appearance* marked by the gipsy descent of *her mother's maternal grandmother* Strong with big muscles and pronounced *universal* myotonia with mechanical myotonia No muscle dystrophy.

21 Girl, daughter of a butcher's assistant, aged 10, *Thomsen's disease. Myotonia from early childhood* Mentally normal *Not* particularly strong *muscles Universal active and mechanical* myotonia No muscle dystrophy

22 Girl, daughter of a journeyman tailor, aged 6 *Thomsen's disease.* The parents observed myotonia in the legs of the daughter when she began walking. The child is mentally *natural*, muscles medium-sized Clear active *myotonia in the legs and mechanical myotonia in the finger extensors.* No muscle dystrophy

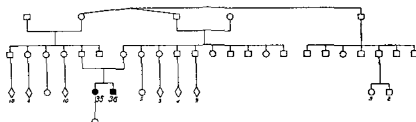
23 Girl daughter of a journeyman tailor, aged 4 *Thomsen's disease.* The parents observed myotonia in the legs of the daughter when, about the age of one, she began walking The child is mentally natural Muscles *very strong, making the child look a small Hercules* Active myotonia in the legs. *Mechanical myotonia impossible to investigate*

Family No 2.

This family has been *traced back* through five generations to a small-holder family on the island of Langeland, Denmark; *the husband was born in* 1790 and the wife in *1805 Their descendants have all left their ancestral soil, and most of them have obtained* a somewhat better position than their forefathers. *Many are* farmers or have married farmers, *some are business men, and a few hold good positions. The family comprises* 204 persons, of whom *165 are living and domiciled in* this country

On account of difficult travelling conditions during the war period the present family has not been investigated so thoroughly as the other four families. To a considerable extent it has been necessary to confine investigations to questionnaires Examined were the patients, their parents, and the child of the sister of the propositus

The disease of the propositus was recognized in the Surgical Department of Viborg Hospital, Jutland

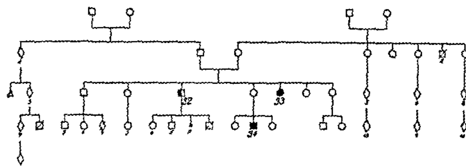


35 Female, m to a warehouse workman, aged 22 *Thomsen's disease.* Myotonia from the age of 6, not aggravated essentially since childhood Myotonia worst after

visible cataract

36 Male, s, farm hand, aged 20 *Thomsen's disease* *Propositus* General myotonia

cataract



32 Male, m., workman, aged 44 *Probably Thomsen's disease.*

33.

34

effect of the quinine treatment, but there seemed to be habituation, and the patient felt no desire to continue the quinine treatment He has served his apprenticeship as a baker and manages well as such

Mentally normal, energetic, and good tempered. Not very tall, but strongly

1945: No cataractous changes (S. L. E.) Cerebrospinal fluid, normal. B M R: 111 to 119 per cent Calcium level 9 9 mg per cent W r : negative.

Family No. 5.

constant down to the present generations, which, however, also include some artisans The family investigation comprises 73 persons, of whom 60 are living and domiciled in this country.

Among those living there are two siblings with Thomsen's disease.

force in the antagonists was the reason for the evidently protracted myotonia at lower temperatures.

These two special phenomena — spontaneous contraction and paresis of the myotonic muscles produced by local subjection to cold — are the characteristic features of paramyotonia.

Schott (1936) investigated the effect of gradual cooling on the muscles of a patient with paramyotonia He was able to demonstrate that when warm the function of the muscle was normal. On subjection to cold the irritability increased, and at the same time active myotonia and myotonic reactions set in, but on increased cooling the irritability, strength, and myotonia gradually decreased, finally giving way to the paretic condition.

The term paramyotonia is applied when — in patients with more or less pronounced myotonia — cooling produces spontaneous tonic contraction of the muscles, and especially when this contraction in spite of subsequent heating is followed by a more or less pronounced paretic condition

Survey of Casuistic Reports

In 1886 *Eulenburg* described paramyotonia in a family from the German Baltic coast It was dominantly hereditary through six generations, in 1916 the pedigree was augmented, and it was then possible to follow the paramyotonia through eight generations without break and without sex-linked inheritance

When for example exposed to a cold wind, these patients experienced a tonic contraction of the orbiculares oculi and oris The paretic phenomena were especially evident in the hands when having remained in cold air or worked with their hands in cold water, the patients were unable to move their fingers for several hours, even if they had been warmed again *Eulenburg* was unable to demonstrate any active or mechanical myotonia Nor did stimulation by faradic current produce any prolonged contraction, but there was clear galvanotonus On very strong cooling almost all muscles grew paretic, and *Eulenburg* compared the condition with paroxysmal familial paresis

Thus, in *Eulenburg's* family there were strongly pronounced paramyotonic symptoms, but only traces of myotonia

In 1894 *Rich* in the U S A described a family of the same character as *Eulenburg's*, but his report has been *inaccessible in this country In Holland, Delprat* (1892), *v d Stock* (1893), and *Sanders* 1 1935 have described a very big family with paramyotonia It can be traced back to 1740, and in 1935 it comprised 74 patients The heredity was of simple dominance As in this family *Delprat* found and described two cases (brothers) with ordinary Thomsen s disease as well as paramyotonic phenomena, he was justified in thinking that paramyotonia was an ailment related to Thomsen's *disease The title of Sander's report of 1935 was*, "*Eine Familie mit* Myotonia congenita (Thomsen'sche Krankheit)", and some authors have, therefore, classified it as Thomsen's disease *Delprat's* and *Sanders* descriptions make it clear that they had before them a family with paramyotonia When in warmer temperatures the patients were completely free from muscle symptoms, but in cold temperatures there was active myotonia in the finger flexors and paramyotonic phenomena in all striated muscles, but most pronounced in the facial muscles After the contracture *there appeared, especially*

CHAPTER IV

PARAMYOTONIA

Simultaneously with Erb's monograph on Thomsen's disease, *Eulenburg* (1886) described a muscle affection, which he termed paramyotonia congenita. The symptoms were produced at lowered temperatures. There was spontaneous contraction of the muscles, followed by a paretic condition lasting for some time. The disease was congenital as well as dominantly hereditary through many generations.

Later authors have described a number of families with syndromes of more or less the same nature, and Table 2 — enumerating the reports of cases of what may be called paramyotonia, including some cases of Thomsen's disease — shows that there is no distinct dividing line between Eulenburg's syndrome and Thomsen's disease. Paramyotonia may, therefore, presumably be regarded as a special variant of Thomsen's disease.

Up to now it has been impossible for this writer to find cases which might be labelled paramyotonia, and his description will, consequently, be confined to a critical survey of published reports.

Paramyotonia.

In the description of Myotonia it has been mentioned how this symptom is influenced by cooling.

In 1923 *Burger & Schellong*, by using electromyography, demonstrated that mechanical myotonia was protracted by cooling. By local application on the skin of ethyl chloride they might produce action potentials, lasting a few seconds — as in mechanical myotonia. It was impossible to produce the same reaction in normal muscles

Nylin (1926) and *Ravin* (1939), using ergometry, demonstrated that the myotonic contraction at 40° C was more protracted than at 20° C. At lower temperatures the strength of the muscles decreased gradually, finally rendering the muscle paretic for a period of 10 to 15 minutes after the muscle has been warmed again. *Ravin* thought that the reduction of

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burg's; and there is a clear continuity from Eulenburg's family to the families with Thomsen's disease mentioned last in the table.

In several of the families the patients had hypertrophic muscles, as in Thomsen's disease (*Sölder, Funcke, Hlawaczek, Sanders*, and *G Koch*).

It must be emphazised that dystrophies in non-muscular organs were noticed in none of the families *Sanders* and *Schott* mention that the intelligence of their patients was good, and that socially they had managed extremely well

Smitt (1938) first tried to treat paramyotonia with paravertebral block but without effect; he then tried daily doses of 100 mg of acetylcholine and reported a benificient effect on the symptoms. This does not sound in itself very probable

Unfortunately this writer has not yet had the opportunity of observing paramyotonia, but a further investigation, *inter alia* with electromyography, of the phenomena would be desirable.

The connexion between the specific cold-phenomena and the myotonia is thus not clear with certainty, but it is possible that paramyotonia is a special symptom attached to myotonia, and especially to Thomsen's disease, so that the pathological picture of paramyotonia in its different variations can be regarded as a syndrome related to Thomsen's disease.

in the muscles of the extremities, a "limp" cramp with loss of power for some hours after the heating All patients in this family had big muscles, but with comparatively reduced strength as in Thomsen's disease.

In *Scholt's* family (1936) there was ptosis in several patients, and one had atrophy in forearms and hands. He made no statements as to atrophy of the sternocleidomastoid muscles or of the non-muscular organs, and the affinity to dystrophia myotonica is, therefore, uncertain

Martius & Hansemann (1889) and *Serog* (1930) described a syndrome, which they named myotonia congenita intermittens When subjected to cold, the patients experienced active myotonia, myotonic reactions, and spontaneous contractures. The contractures were not followed by paresis

There have been published reports of a number of cases with symptoms of Thomsen's disease and paramyotonic phenomena in cold temperatures

Several authors have called their reports "Paramyotonia", although they have nothing to do with this disease [*Gower* (1892), *Kiesewalter* (1897), *Dercum* (1900), *Bumke* (1911) and *Gordon* (1923)]

Table 2

			After subject to cold				At normal temp			
	Congenital	Dominant heredity	Spontaneous contracture	Paresis	Mechanical-electrical myotonia	Active myotonia	Mechanical-electrical myotonia	Active myotonia	Thomsen's disease in the family	
Eulenburg 1886	+	+	+	+	(+)	—	—	—	—	
Alsberg 1898		+	+	+	+	—	—	—	—	
Lewandowsky 1916		+	+	+	+	—	—	—	—	
Solder 1895		+	+	+	++	—	—	—	—	
Delpratt 1891, v d Stock 1893 and Sanders 1935		+	+	+	++	+	—	—	+	
Schott 1936		+	+	+	++	+	+	—	—	*Muscle atrophy in some cases*
Martius & Hansemann 1889	(+)	+	+	—	++	+	—	—	—	
Serog 1891	+	+	+	—	++	+	—	—	—	
Frus 1891		+	+		+	+	+	+	+	
Hlawaczek 1896	+	+	+		+	+	+	+	+	
Funcke 1898		+	+	?	+	+	+	+	+	
Hubner 1917		+	+		+	+	+	+	+	Myopathic facies
Smitt 1938		+	+		+	+	+	+	+	
G Koch 1943		+	+	+	+	+	+	+	+	

In Table 2 I have made a survey of reported cases of paramyotonia and of cases of Thomsen's disease with definite paramyotonic symptoms.

There are, as will be noticed, but few reports of paramyotonia. In all cases there is dominant heredity, and the disease has been present from the very earliest childhood; thus, it may possibly be congenital.

The myotonic phenomena were more or less pronounced — but possible of demonstration — in all families, although very weak in *Eulen-*

4. Finally, there is a group of 12 patients who are not likely to have had myotonia: *Talma* (1892) II, IV, V, *Fürstner* (1895), *Jacoby* (1898) II, *Dercum* (1900), *Haenel* (1902), *Walton* (1902), *Bechterew* (1905), *Jaquemart* (1908), *Salzberger* (1910), and *Wagner* (1918).

As, in my opinion, *Krabbe's* patient, a description of whom will be given later, did not have myotonia, the conclusion must be that the investigations reported up to the present moment cannot be considered a sufficient basis for the differentiation of a special group of diseases with the name myotonia acquisita

CHAPTER V

MYOTONIA ACQUISITA

In 1892 *Talma* introduced this term to designate a myotonic syndrome without demonstrable heredity and with acute manifestation at adult age.

Krabbe (1934) was the last to use the designation myotonia acquisita to cover a non-hereditary, acutely developed disease with muscle hypertrophy and myotonoid functional disturbances. The syndrome had developed after an infection or an intoxication and showed a tendency to subsequent improvement.

Krabbe found, in the works of other authors, 34 reports of myotonia acquisita, but his survey of the clinical descriptions may not be characterized as critical

Ravin (1939) took up a very sceptical attitude towards the myotonia acquisita conception, and although he would not categorically deny its existence, the disease was, in his opinion, extremely rare.

A survey of *Krabbe's* 34 above-mentioned cases reveals many of the casuistic reports to be supported by such insufficient clinical examinations that it is difficult to decide whether the functional disturbances were of myotonic nature. In some cases the authors have completely misunderstood the term myotonia, as they applied it to spastic or cramp-like conditions with pains.

In the opinion of this writer, the cases may be sorted into four groups:

1. Cases which were presumably dystrophia myotonica: *Talma* (1892) I, *Hoffmann* (1896), *Kornhold* (1897), *Schoenborn* (1899), *Voss* (1908), *Fuchs* (1909), *Grund* (1911), and *Faure-Beaulieu & Deschamps* (1923).

2. Cases in which myotonia has been demonstrated with some probability, but where the clinical description is too incomplete to make it possible to decide whether it was e.g. dystrophia myotonica: *Rybalkine* (1892), *Jacoby* (1898), *Erben* (1910), *Jeanselme & Huet* (1916), *Wexberg* (1917), and *Rimbaud & Jourdan* (1922).

3. Cases where the clinical descriptions are insufficient for judging of the existence of myotonia· *Talma* (1892) III, *Nartowski* (1900), *Trömmer* (1912), *Beco* (1914), *Huet & Francais* (1916), and *Abrahamson* (1920).

muscle hypertrophy and myotonoid functional disturbances are, on the other hand, most often found in adults and may be termed Hoffmann's syndrome.

MYXEDEMA WITH MUSCLE HYPERTROPHY AND TARDY MUSCLE FUNCTION

Debré-Semelaigne's Syndrome.

Kocher (1892) drew attention to the fact that in sporadic cretinism and in cachexia strumipriva there might be found muscular changes with voluminous musculature, comparatively reduced strength, and slow, tardy movements This condition might be found with or without tetany, and had not been previously described

There is a series of casuistic reports of this special syndrome in myxedema Most of the patients were children, and the designation Debré-Semelaigne's syndrome has especially been applied to the syndrome in children (Table 4).

Bruck (1889) described a girl of 10 months who was an idiot and had immense diffuse muscle hypertrophy with macroglossia, rigid muscles and, at times, muscle spasms with opisthotonos Reflexes and electrical reactions in the muscles were normal The child died and autopsy revealed hypertrophy of smooth and striated musculature, but no other abnormalities, especially not in the C N S He made no observations as to the thyroid gland

Langhans (1897) described a cretin of 14 months, who looked like a small athlete with contracted muscles The child died At autopsy the muscles were found to be remarkably pale yellowish-white, and the single muscle fibres were blown up with a long distance between the Cohnheim's fields

Dieterle (1906) demonstrated the syndrome in a girl of 4, who died on account of growing cachexia The hypertrophic muscles were remarkably pale, and the thyroid gland insufficiently developed

Cornelia de Lange (1934) described congenital muscle hypertrophy with hypertonia in three infants and she thought she was dealing with a new syndrome, caused by a congenital defect in the striatum At autopsy of the first patient she found external hydrocephalus and porencephalia and thought that the two others had similar changes in the brain It is probable that number three had Debré-Semelaigne's syndrome Although the patient had rough voice and big tongue as in congenital myxedema, she nevertheless thought that the muscular changes were due to brain defects as found in the autopsied infant

Debré & Semelaigne roused interest by their description of the syndrome in two children and their effective treatment with thyroidin

The first patient was a boy of 10 months with myxedema, arrested growth, and diffuse muscle hypertrophy with hard muscles He died within a short time, untreated

The other patient was a girl of 2, whose growth stopped a few months after her birth She had myxedema, was almost an idiot and had pronounced diffuse muscle hypertrophy with hard muscles with slow and weak movements She was treated with

CHAPTER VI

MYXEDEMA WITH MUSCLE HYPERTROPHY AND MYOTONOID FUNCTIONAL DISTURBANCES

Hoffmann's Syndrome.

French authors, especially, have during the last decade taken interest in certain muscular changes to be found in cases of myxedema. Characteristic of these are an increased volume of muscles and a tardy, slow muscle function, which in a number of cases resembles, and has been *regarded as, myotonia. The muscular changes are found clearly pro*nounced only in few cases of myxedema. They become manifest at the same time as the myxedema and can be made to disappear when treated with thyroidin preparations; to all appearance they are closely connected with the metabolic disease.

Several authors have regarded the myotonoid muscular functional disturbances as true myotonia, wherefore in many cases treatment of true myotonia has been attempted with thyroidin.

This writer had a patient, who had previously been diagnosed myotonia acquisita, but who presented the myotonoid muscle syndrome in myxedema just described. This syndrome I have termed Hoffmann's *syndrome, as Hoffmann (1897) was the first to describe it clearly.*

Muscular Changes in Myxedema.

In myxedema the muscles are ordinarily limp, powerless, but without morphological changes. In a few cases there is a variant clinical picture with hypervoluminous muscle development and a remarkably tardy and slow muscle functioning, which in certain cases may be called myotonoid.

Myxedema with muscle hypertrophy is especially found in children and is frequently called Debré-Semelaigne's syndrome. Myxedema with

muscle hypertrophy and myotonoid functional disturbances are, on the other hand, most often found in adults and may be termed Hoffmann's syndrome

III

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The other patient was a girl of 2 whose growth stopped a few months after her birth She had myxedema was almost an idiot and had pronounced diffuse muscle hypertrophy with hard muscles with slow and weak movements She was treated with

2 cg of thyroidin daily, which in six months had a surprising effect The myxedema as well as the muscle symptoms disappeared and the mental condition became almost normal.

Hall, Sunderman & Gittings (1936) found the muscular changes present in an infant, whose B M R was 88 per cent; it had abnormally large excretion of creatine as well as of creatinine in the urine When, at the age of 17 months, they did not find delayed ossification they did not consider the child to have myxedema, and did not treat it with thyroidin This patient suffered from protruding sphincter ani on account of hypertrophy — a symptom also noticed by *Bruck* and *Dieterle*.

Darré, Mollaret, Zagdoun & Oehmichen (1939) described the syndrome in a girl of 5 months with B M R of 55 per cent. By radiography it was possible to demonstrate thickening of the intestines and ventricle wall. Not until after three months' treatment with increasing doses of thyroidin did they find any improvement in myxedema as well as in muscular symptoms

Wertz (1931) described the syndrome in a male of 44, with myxedema following strumectomy. Apart from the symptoms previously mentioned he had diffuse muscle pains All symptoms disappeared when treated with thyroidin.

Hesser (1940) found the syndrome in a female of 30, who, alongside with the development of myxedema, had painful diffuse muscle hypertrophy, which disappeared when treated with thyroidin and returned by discontinuation of the treatment

These cases of myxedema have in common hypertrophic hard muscles, slow and tardy movements. In adults there are, further, diffuse muscle pains. Thyroidin was administered to four patients in all, — in each case with complete curative effect on the muscular syndrome.

MYXEDEMA WITH MUSCLE HYPERTROPHY AND MYOTONOID FUNCTIONAL DISTURBANCES

Hoffmann's Syndrome

Hoffmann (1897) found — besides the muscular changes described by Kocher (1892) — myotonoid functional disturbances in a patient several times operated for struma. The patient was a male of 18 who simultaneously with the myxedema had pains and a feeling of tension in his very big muscles. There was a certain tonic tension in the muscles, but no hampering of passive movements Contracture of the biceps brachii might occur and the first steps after rest were stiff and clumsy After biting he might have difficulties in opening his mouth, but these disappeared upon repetition of the movement. The extremities displayed similar phenomena, but even after repetition of the movements there was a certain degree of fatigue and tension left. The patient had latent tetany, but, in Hoffmann's opinion, without connexion with the myotonoid functional disturbances just described. On the other hand he realized that the muscular symptoms did not completely resemble those of Thomsen's disease, e g in that after repetition of movements there remained evident signs of fatigue and stiffness

Table 4

Debré-Semelaigne's Syndrome.

	Author	Age	Sex	Myxedema	Muscle hypertrophy	Muscle stiffness	Active "myotonia"	Mechanical or elect "myotonia"	Thyroidin treatment
1	Bruck 1889	10 m	f	(+)	+	+		—	—
2	Langhans 1897	14 m		+	+				
3	Dieterle 1906	4 m	f	+	+	+			—
4	Cornelia de Lange 1934	4 m	m	(+)	+	+	—	—	—
5	Debré & Semelaigne 1935	10 m	m	+	+	+	—	—	—
6	Debre & Semelaigne 1935	2 ys	f	+	+	+	—	—	+
7	*Hall, Sundermann & Gittings* 1936	1 m	m	+	+	+	—	—	—
8	Darré, Mollarét, Zagdoun & Oehmichen 1939	5 m	f	+	+	+	—	—	+
9	Weitz 1931	44 ys	m	+	+	+	—	—	+
10	Hesser 1940	30 ys	f	+	+	+	—	—	+

Hoffmann ascribed the syndrome to strumectomy and rather considered it to be on the same line as the latent tetany, the cause of which was at that time attributed to the removal of the thyroid gland. He therefore, with great success, treated it with thyroid preparation, following which treatment the myxedema as well as the muscle changes disappeared

When bearing in mind that only thirteen years had passed since the publication of *Erb's* monograph on Thomsen's disease, one must admire *Hoffmann's* critical attitude towards the myotonoid symptoms in his patient.

Hoffmann's syndrome has been reported in children as well as in adults (Table 5)

Hoffmann's Syndrome in Children

Carrière (1906) described the first case in a report entitled "Macroglossie congénitale et syndrome de Thomsen, dus à l'hérédo-syphilis" The patient was an infant of 11 months, the mother had had two miscarriages, and *Carrière* therefore imagined the possibility of congenital syphilis The infant had macroglossia and was Herculean with tardy movements At the movements there was initial and terminal spasmodic stiffness, less pronounced in heat At electrical stimulation there was slow contraction and prolongation for 1 to 5 seconds The patient was treated with thyroidin, and the muscle symptoms disappeared completely

Slauck (1921) in a boy of 4½ years found infantile myxedema and hypertrophic musculature Electrical stimulation with faradic and galvanic currents produced an increasingly retarded contraction, and after discontinuation of the stimulation, a persistent decreasing contraction of a tonic nature *Slauck* himself however, only with

some reserve compared these muscular symptoms with myotonia There is no mention of thyroidin treatment

Valdez-Diaz (1932) described a negro infant, who, in his opinion, had myotonia congenita The infant displayed universal muscle hypertrophy with Herculean appearance, general muscle stiffness, and mechanical, but not electrical, myotonia There were no familial cases Following Hoffmann's example he administered thyroidin with a curative effect on the muscular symptoms

Denoyelle, de Grailly & Giraud (1933) treated a boy, who had Hoffmann's syndrome ("Petits signes myotoniques") Since the age of one the boy had had hypertrophic muscles and slow, tardy movements Having caught hold of an object, he could let go only with great difficulty Treatment at the age of 3 with large doses of thyroidin made myxedema and mucular symptoms disappear whereby his mobility became free

Poncher & Woodward (1936) found the syndrome in an infant boy of 5 months, who, in their opinion, had myotonia congenita The tongue was too large. There was delayed development and the infant had a blown-up appearance with muscle hypertrophy Stimulation of the muscles with galvanic current produced slow, wormlike contraction which persisted for almost one minute after the discontinuation of the stimulation

As in hypothyroidism, the physiological creatinuria was lacking, but ossification was normal and they therefore did not believe the infant had myxedema They nevertheless administered thyroidin, and after five months the infant was completely cured of its "myotonia congenita" When the authors then discontinued the thyroidin treatment the child again grew stiff with myotonoid reactions, and the creatinuria was reduced

Hoffmann's Syndrome in Adults

After *Hoffmann* (1897), *Shmidt* (1903) reported a similar symptom in a male patient, age 40, with myxedema and without familial cases of Thomsen's disease. Shortly after the myxedema had become manifest at an adult age muscle spasms took place on active movements and, later, "typical myotonia" Myxedema as well as muscle symptoms yielded to thyroidin treatment, but temporarily returned when the treatment was discontinued for some time There are no remarks of muscle hypertrophy in this patient

Kramer (1917) described three adult patients under the designation "Ungewohnliche elektrischer Befund bei Muskeldystrophy" In 1918 *Zondek* augmented *Kramer's* description of the muscle symptoms with the information that the patients had myxedema with its usual symptoms Besides myxedema they all three had muscle hypertrophy with slowness of movements, speech, and reflexes There was no active myotonia but occasionally mechanical myotonia *and delayed relaxation upon faradic stimulation* Thyroidin treatment during some weeks made all symptoms disappear

Garcin, Rouquès, Laudat & Frumusan (1935) headed a series of French reports of Hoffmann's syndrome The title of their work was· "Syndrome thomsénien et syndrome myxédémateux cliniquement associés Début simultané et évolution parallèle" About the same time *Garcin & Bourguignon* gave an account of the electrical examinations and *Garcin & Bertrand* described [illegible] ic inves[illegible] after the patient had died of pulmonary tuberc[illegible] 28 [illegible]

Myxedema and the so-called myot[illegible] y [illegible] 25. There was diffuse muscle hypertrophy [illegible] Following rapid movements there might be pa[illegible] spasms [illegible]sion in the muscles After [illegible] declenching t[illegible] laxation, [illegible] upon

repetition There were similar symptoms in the lower extremities The authors were not completely convinced of the quality of the myotonia, as they described it in these terms "Une contraction traînante suivie d'une décontraction lente, du type de myotonie légère" Relaxation took only three seconds as compared with ten seconds in Thomsen's disease, and the chronaxia was reduced There were no opportunities for thyroidin treatment as the patient died

Bertrand at histological examination found enlarged diameter of the muscle fibres on account of increased quantities of sarcoplasm

Nevin (1936) personally communicated to *Poncher & Woodward* a case of Hoffmann's syndrome in a girl of 17 who had cretinism, muscle hypertrophy, and "myotonia" At *electromyography* he did not find the same conditions as in Thomsen's disease, wherefore he doubted the diagnosis of myotonia

Mollaret & Sigwald (1939) described the syndrome in a male of 51 with acquired myxedema In the course of two months he contracted a considerable degree of muscle hypertrophy accompanied by muscle pains and firm, tense muscles There were short muscle cramps and strength was clearly reduced There was no mechanical myotonia, and the reflexes were normal

Bourguignon found very localized electrical myotonia in the right biceps brachii muscle, and in most of the other muscles there was slow contraction and galvanotonus ("petite myotonie") which was essentially aggravated when exposed to cold All except the myotonic symptoms in the right biceps muscle yielded to thyroidin treatment

Table 5

Hoffmann's Syndrome.

	Author	Age	Sex	Myxedema	Muscle hypertrophy	Muscle stiffness	Active "myotonia"	Mechanical or elect "myotonia"	Thyroidin treatment
11	Carrière 1906	11 m		(+)	+	+	+	+	+
12	Slauck 1921	$4^1/_2$ ys	m	+	+	+		+	
13	Valdez Diaz 1932	1 m	m	(+)	+	+		+	+
14	Denoyelle de Grailley & Giraud 1933	1 ys		+	+	+	(+)	—	+
15	Poncher & Woodward 1936	5 m	m	+	+	+		+	+
16	Hoffmann 1897	18 ys	m	+	+	+	+	+	+
17	Shmidt 1903	40 ys	m	+		+	+	+	+
18	Kramer 1917	30 ys	m	+	+	+	—	+	+
19	— —	30 ys	m	+	+	+	—	+	+
20	— —	30 ys	m	+	+	+	—	+	+
21	Garcin, Rouquès, Laudat & Frumusan 1935	25 ys	m	+	+	+	+	+	—
22	Nevin 1936	17 ys	f	+	+	+	+	+	+
23	Mollarét & Sigwald 1939	51 ys	m	+	+	+	—	+	+
24	Mollarét & Rudaux 1939	35 ys	f	+	+	+	+	+	+
25	Maas & Paterson 1939	20 ys	f	(+)	+	+	+	+	+
26	Lenègre & Huguenin 1941	52 ys	f	+		+	+		+
27	Thiébaut & Henrot 1943	31 ys	f	+		+	+	+	+
28	Thomasen 1945	40 ys	m	+	+	+		(+)	+

In the following year *Mollaret & Rudeaux* (1939) reported a case of rapidly-developed myxedema with muscle hypertrophy and myotonoid phenomena. The patient was a woman of 35 who during one and a half months felt growing muscle hypertrophy *and swelling of the muscles, accompanied by stiffness and pains* Her muscles were hard, there was delayed relaxation after hand-shake and improvement upon repetition Electrical examination revealed galvanotonus in certain muscles Cooling aggravated the symptoms, whereas heat had a beneficient effect on the stiffness Thyroidin treatment made all symptoms disappear. Later the patient discontinued the treatment, and the symptoms returned [*Mollaret & Beau* (1941)].

Maas & Paterson (1939) reported that they had noticed a similar syndrome in a female of 20 with hypertrophic muscles She had electrical, mechanical, and active myotonia All muscle symptoms disappeared completely following thyroidin treatment

Lenegre & Huguenin (1941) described the syndrome in a female of 52 with myxedema after roentgen treatment of the neck There was no pronounced muscle hypertrophy, but all muscles were visible through the skin and felt firm Walking was stiff and slow with tense muscles, and relaxation was protracted

Thyroidin treatment during two months cured the patient of myxedema as well as of muscle symptoms

Thiébaut & Henrot (1943) reported the syndrome in a female of 31 who had had myxedema for some years She had no muscle hypertrophy, but stiffness and pains when moving the hip joint, and cramps at certain movements in cold temperatures, besides, slight retardation of relaxation, for example when opening the hand She had mechanical myotonia in the thenar muscle and there was widespread galvanotonus

Myxedema as well as muscular changes completely disappeared when treated with thyroidin

Own Case

The disease of this patient has been reported by *Krabbe* in 1933, diagnosed as myotonia acquisita following polyneuritis. It is my intention to demonstrate that *Krabbe's* patient already in 1932 had — in my opinion — symptoms which justified the diagnosis of Hoffmann's syndrome

Male, aged 40, who at the age of 28 was treated at the Neurological Ward of the Kommunehospital, Copenhagen (Case Book 350/32)

Mother and two sisters have had slight Basedow's disease. No known familial cases of myxedema or muscle ailments

Lesion of left heel with inflammation when aged 16 Tetanus during the course of the disease, treated with intramuscular and intraspinal injections of antitoxin From that

[illegible] hip

[illegible] almost all

muscles, but without fever Simultaneously the muscle swelled, making him appear like an athlete, and he had to use a far larger collar size He felt increasingly tired and gladly made a détour to avoid lifting his legs over a fence a couple of feet high Walking up stairs he had to use his hand in support His previously rapid movements grew slow and tardy, and even the tongue could not "follow the brain," and his speech might become indistinct if he did not speak slowly The tardiness manifested itself at contractions and at relaxations and was especially pronounced at cooling In a warm bed or in a hot bath his movements were much freer; as they also were when he was

warm as the result of work Besides the muscular tardiness he felt certain mental hamperings with indolence and depression, and he had difficulty in getting his work done. Finally, he noticed reduced sweat secretion and increased sensitiveness to cold, especially pronounced in hands and feet

At the Neurological Department of the Kommunehospital, Copenhagen, when he was 28, diffuse muscle hypertrophy was found, strength of all muscles being good, though not corresponding to volume of muscles, tone normal, Trousseau's and Chvostek s signs were absent

All movements were carried out with considerable slowness, and there was pronounced tardiness, e g at the diadokokinetic test All tendon reflexes were somewhat weak Sensibility was normal, and there were no co-ordination disturbances Walking natural

On the left heel was found a fistulous opening The inversion-eversion of the foot were suspended and the hypertrophy of the left calf muscle was less than of the right

Electrical investigation revealed reduced sensitiveness to faradic and galvanic current Following stimulation by faradic current there was found, as it is expressed "clear myotonic reaction with slow relaxation and a faint suggestion of waves" These phenomena were most pronounced in the gastrocnemius muscles and varied somewhat at the different examinations

On cooling there was strong reduction of sensitivity to faradic current with simultaneous decrease of muscle strength Galvanotonus could not be demonstrated The "myotonic reaction" upon faradic stimulation was unaffected by cooling, nor was it changed after the patient had walked for three hours Acetylcholine, subcutaneously, produced no effect Hand-shaking was not of a myotonic nature

The patient s features were coarse, his voice rough, his skin was yellowish and pale with deep wrinkles, eye openings were narrow Pilosity on the head was strong, but the skin dry all over Genitalia were normal

It was impossible to palpate the thyroid gland *B M R* at repeated examinations 67 per cent Pulse 44

There was complete achylia, and blood sugar when fasting was 79 mg per cent Serum calcium 10 7 mg per cent, lactic acid in blood normal

C S F 2 to 3 cells per ccm , proteine slightly increased W r and Kahn's test no reaction in blod or cerebro-spinal fluid

Vision $^6/_6$ O U Ophthalmoscopy normal, and there were no cataractous changes at slit lamp examination

Biopsy of the right crus showed slight increase in the volume of the muscle fibres Here and there were found nuclei centrally in the muscle fibres, but there were no lipoid infiltrations or signs of inflammation

Krabbe thought that here was a case of myotonia, partly because of the muscle hypertrophy and partly on account of the "myotonic" reaction.

The patient was treated with thyroidin (200 units × 3), whereupon he felt better and gained more strength The volume of his muscles seemed to decrease, but despite this therapeutic result *Krabbe* only in passing considered the possibility that it was the hypothyreosis that caused the muscular phenomena.

Since 1932 he received almost constant daily doses of 200 units of thyrodin, as he felt he needed it. The treatment somewhat reduced the

muscle fatigue and he felt less hampered and depressed. Especially in winter he was, however, still inconvenienced by tardiness and cold

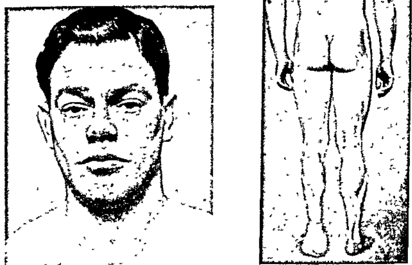


Fig 7

Myxedema and Hoffmann's syndrome Photographs taken before efficient thyroidin treatment (1940)

Own Investigation 1940.

His appearance almost corresponded to the photograph of 1932, and the development of his muscles was approximately the same with general pronounced hypertrophy, especially evident on back and extremities The subcutaneous fat tissue was sparse, and the muscle bellies were clearly delienated through the skin

His face was pale, yellowish, somewhat thickened round the eyes, which had narrow openings The skin on his forehead was coarsely wrinkled, and his lips were thick There was no clear atrophy of the skin on hands and feet, but it was cool and dry Hair of the head, axilla, and pubes were coarse, but sparse Genitalia were natural

His voice was hoarse and deep, speech slow Once, when he came in from cold weather, his speech was indistinct because the tongue was somewhat stiff

There was no active myotonia In cold he felt somewhat stiff with tardy movements, and the muscles, when touched, were firm not to say hard After having stayed in a warm room for some time his movements became freer and the muscles softer.

Strength of hand-grasp comparatively adequate· 60 kg in both hands

Percussion of the muscles nowhere revealed mechanical myotonia, but there was idiomuscular reaction in upper arms and forearms and in the flat muscles of the back

At electrical examination with faradic, strong current of the lateral head of the right gastrocnemius muscle the first contraction remained for 1/2 to 1 sec after the current had been switched off This protracted contraction gradually became shorter, but could still be registered at repetition of the stimulation There was no galvanotonus, and sensitivity was reduced, as it was necessary to employ 10 to 12 ma to obtain contraction

Tendon reflexes were medium without retardation of the reflex movement Sensibility was normal

Fistula on left heel Roentgenography showed local ostitis and synostosis in the subastragular joint

Ecg showed low voltage in all leads with almost total extinction of all waves in lead III The frequency was very slow Otherwise the ecg was normal

B M R was 74 per cent with very slow respiration (39 over a period of 10 minutes) He had received no thyroidin treatment for three weeks prior to this test

All other investigations gave the same results as in 1932

Thus, the results obtained at my clinical investigations were almost the same as those found by *Krabbe* in 1932, even if the symptoms were slightly more pronounced at that time — before the patient had begun thyroidin treatment

In 1932 there were not observed symptoms of what might be called clear active myotonia, but in *Krabbe's* conception the tardy movements were signs of myotonia The electrical myotonia was doubtful in 1932 and in 1940, as it was impossible to produce galvanotonous, and only a very inconsiderable protraction of the contraction upon faradic stimulation. Nor does reduced sensitivy make the diagnosis myotonia convincing

In 1940 I supplemented the clinical investigation by electromyography The electrical activity during voluntary contraction was normal There was no prolonged activity after voluntary contraction, nor after mechanical stimulation — i e there were no electromyographical signs of myotonia

Own Investigation 1944

Since 1940 the patient has constantly taken daily doses of 400 units of thyroidin (4 mg of thyroxin), and he feels completely well on these doses He has been operated on for calcaneal ostitis and the wound has healed

In 1944 there were no symptoms of myxedema His face had become normal and his voice was no longer hoarse B M R was 110 per cent, serum cholesterol 155 mg per cent, and apart from sinusbradycardia (45) the ecg was normal

His muscles were strong but not as previously hypervoluminous There was no muscle fatigue and his movements in cold temperatures were rapid

The patient could now stand a cold bath and he felt completely recovered

The conclusion from these investigations is that the patient did not have myotonia in 1940. As there are only differences in degree between the pathological pictures of 1932 and of 1940 it is not likely that the patient had myotonia in 1932.

The pathological picture with myxedema, acutely appearing muscle hypertrophy with tardy and myotonoid muscle functioning, completely covers Hoffmann's syndrome as described above. All symptoms yield to efficient thyroidin treatment, and this fact may be taken as a further proof of the correctness of this view.

SUMMARY

Descriptions have been given of 28 patients with myxedema and muscular symptoms in the form of muscle hypertrophy (10) or muscle hypertrophy and myotonoid symptoms (18). Of these 18 the majority has hitherto been classified as having myotonia or Thomsen's disease. The syndrome in my own patient has previously been reported as myotonia acquisita

In reports published up to the present, myxedema has been described with greater or lesser skill. Some authors have investigated for tetany and have determined the serum calcium levels. These were invariably normal, and apart from *Hoffmann's* patient, who had myxedema alongside with latent tetany, there were no cases with clinical signs of tetany.

Like my own patient, many complained of muscle pains at the onset of the disease, and in particular some had painful muscle cramps. These muscle pains are likely to be the reason why *Krabbe* thought that his patient had polyneuritis, although there were no definite neurological deficiency phenomena

In practically all cases there was muscle hypertrophy to a considerable degree, and in some cases this hypertrophy developed in the course of a few months. Simultaneously there was fatigue and tardiness of movements, and the muscle strength was often reduced

Muscle biopsy in some cases revealed thickened muscle fibres with ample sarcoplams, but there was no constant hypertrophy of the fibres. In some patients the tardiness of movements gave the impression of myotonia, as the contraction was protracted several seconds, and in some cases it was possible to demonstrate the same phenomenon by mechanical and electrical stimulation Several authors, who especially investigated this Hoffmann's syndrome did, however, realize that these reactions were different from the true myotonic reactions.

My investigation has shown that *Hoffmann's* syndrome cannot be characterized as myotonia, but is a syndrome which must come into consideration as a differential diagnosis in relation to Thomsen's disease.

CAUSE OF MUSCULAR CHANGES IN MYXEDEMA

Soderbergh (1912), in certain cases with myxedema, besides slow muscle functioning found adiadokokinesia and possibly asynergy and gyratory dizziness. He therefore thought that the origin of the muscular functional disturbances were to be sought in functional changes in the cerebellum

Similar "cerebellar" functional disturbances have been reported by *Eckerström* (1936), who in addition found strikingly slow Achilles tendon reflexes In 1924 this same observation had been noted by *Chaney* who thought that a general reduction of cellular activity in myxedema caused the slowness of movements *Marinesco* (1919) demonstrated such reduced cellular activity in four patients with myxedema, he found reduced body temperature, and very low temperature of the muscles (29 to 30 centigrades) At this low temperature the functioning was tardy and slow, but grew livelier upon heating *Marinesco* compared patients with myxedema with poikilothermal animals. *Mussio-Fournier* (1933) stressed the importance of *Marinesco's* investigations and demonstrated that the reflexes were more rapid than normal in patients with hyperthyreosis

Marinesco's explanation of the muscular tardiness and stiffness must be considered the more probable There seems to be no reason for the assumption that the cerebellum is affected as the tardy movements may explain dysdiadokokinesia, dysmetria, and cerebellar ataxia. The muscles *do not follow the speed of the will* "*The tongue cannot follow the* thoughts " As far as can be seen the myotonoid symptoms are produced by this muscle tardiness

Until further it is not possible to offer an explanation of the muscle hypertrophy, but it is out of the question that it can be any genuine hyperplasia or hypertrophy, rather it may be an edematous swelling of the muscle fibres It would, in my opinion, be impossible for hyperplasia or hypertrophy to vary in the course of days and weeks, depending on the treatment

CHAPTER VII

DYSTROPHIA MYOTONICA

A. HISTORY

Erb's monograph of 1886 roused the interest in myotonia, and during the following years there appeared a number of reports on the disease. The majority were on Thomsen's disease, so thoroughly described by *Erb*, but towards the end of the century several reports were published on myotonia with more or less pronounced, localized muscle atrophy.

The first certain description of dystrophia myotonica was published by *Hoffmann* in 1896. Its title was "Ein Fall von Thomsen'scher Krankheit complicirt durch Neuritis multiplex."* It is likely that the myotonia set in at the age of 8, but when 33 the patient experienced increasing weakness of both hands accompanied by muscle atrophy. *Hoffmann* pondered this strange, symmetrical muscle atrophy — there were no disturbances of sensibility — but the patient had a propensity to drink and was mentally deficient, for which reason *Hoffmann* supposed that it was a case of Thomsen's disease complicated with neuritis.

Four years later *Hoffmann* (1900) was able to report a similar pathological picture in two siblings, who from the age of 25—30 had myotonia in the finger flexors, then atrophy of facial muscles, mastication muscles, sternocleidomastoid muscles, flexors of forearms, and in the small muscles of the hand. The atrophies were symmetrical, progressive, and not accompanied by fibrillation or disturbances of sensibility. There were no remarks as to non-muscular organic changes, and the psyche was natural.

Besides these two excellently described patients there had been reported a number of cases with Thomsen's disease complicated with muscular atrophy [*Pelizaeus* (1897), *Kornhold* (1897), *Hammond* (1898), *Bernhardt* (1899), *Nouguès & Sirol* (1899), and *Schoenborn* (1899)], but in these cases the atrophies were not typically localized. In 1900

* "A Case of Thomsen's Disease complicated with Neuritis Multiplex."

Hoffmann, therefore, found it impossible to form an opinion of the favourite site of origin of the atrophies.

Despite an increasing number of reports with more accurate descriptions of Thomsen's disease complicated with myatrophy [*Gaup* (1900), *Rossolimo* (1902), *Hoffmann* (1903), *Berg* (1904), *Mannel* (1905), *Curschmann* (1905), *Lannois* (1905), *Hoffmann* (1906), *Curschmann* (1906), *Fürnrohr* (1907), *Hunt* (1908), *Voss* (1908), *Fuchs* (1909), and *Chvostek* (1909)], none succeeded in finding what might be called the common denominator Even in 1905, *Curschmann* expressed the opinion that it was impossible to observe any typical localization of the atrophies. Common features of several of the reports were familial occurrence and comparatively late onset

Rossolimo's term for this deviating type of Thomsen's disease was myotonia atrofica — a name which was soon adopted by most authors

Batten & Gibb (1909) found the atrophy most frequently localized in the facial and sternocleidomastoid muscles, the muscles of the forearms, and, more rarely, in the quadriceps femoris and the muscles on the anterolateral side of the leg This localization was of so specific a nature that it — to an equal degree as the myotonia — placed the disease in a class of its own In their opinion there must, therefore, exist a special form of myopathia, characterized by the definite localization of the dystrophies and combined with myotonia

In the same year *Steinert* (1909) published the work that made it clear that here was a specific disease, different in nature from Thomsen's disease, as besides muscular dystrophies there were other organic dystrophies as well. The title of his work was "Über das klinische und anatomische Bild des Muskelschwunds der Myotoniker" By investigation of his own six cases, besides those of the literature on the subject, *Steinert* was able to demonstrate a favourite site for the atrophies of the muscles of the forearm, the sternocleidomastoid muscles and those of the face

Apart from these favourite sites of origin, the atrophies might, in severe cases, affect most muscles. *Steinert* further stressed a number of characteristic features of the disease e g. the comparatively frequent bulbar paresis with disturbance of speech and possibly swallowing difficulties, the ptosis and the tendency to jaw dislocation because of atrophy of the mastication muscles

Most important, however, was his demonstration of the non-muscular organic dystrophies with baldness, atrophy of testes reduced potency and vasomotor disturbances with acrocyanosis Like a number of previous authors he further in some patients demonstrated slight uncharacteristic sensibility disturbances distally on the extremities.

Steinert himself was in doubt as to the interpretation of these cases of atrophic myotonia, but he still thought that they were cases of Thomsen's disease, in which had developed a specific *myotonia-dystrophy.*

Steinert described the pathologico-anatomic finds in a patient, who, *inter alia*, had suspended patellar and Achilles tendon reflexes. On autopsy and histological examination of the spinal cord he found degeneration of the posterior funiculi. On the basis of this histological find and the frequently absent tendon reflexes in these patients, he was forced to conclude that the degeneration of the posterior funiculi was typical of the disease. Not until later was it realized that *Steinert's* find was purely accidental.

In 1910 and 1911 *Steinert* was able to augment his preliminary report by a description of menstruation disturbances as a symptom of the disease; then no more is heard of him. There is an obituary mention of him in *Curschmann's* work from 1912.

As *Thomsen's* first work was corroborated and publicized by *Erb* in 1886, so *Steinert's* report received its confirmation in *Curschmann's* work from 1912. He here underlined that Steinert's disease presented a distinctly defined clinical picture, which admittedly was related to, but not identical with, Thomsen's disease.

Curschmann expressed his surprise that during five previous years he had not observed one single case of dystrophia myotonica, whereas during the eighteen months since the publication of *Steinert's* first work he had seen six cases of myotonia with atrophy. He was therefore somewhat doubtful as to the reliability of the many reports on Thomsen's disease up to that time.

Curschmann indicated clearly the differences between *Thomsen's* disease and *Steinert's* disease. Firstly, *Steinert's* disease invariably set in in later life, generally between the ages of twenty and thirty. Further, the myotonia was almost stereotypically localized so that the term rudimentary myotonia was justified, and this was also the case with the myotonic reactions. The most essential distinction, however was the typical muscle atrophies and the non-muscular organic dystrophies, not found in Thomsen's disease.

Curschmann showed that the muscle dystrophies could not be the sequence of myotonia, as they frequently appeared in muscle groups that had never presented active myotonia, and in no few cases muscle dystrophy became manifest before myotonia.

Curschmann's description of the non-muscular organic dystrophies were somewhat more thorough than *Steinert's*, and especially *Curschmann's* picture of the "C 3 wretches" cannot but leave upon the memory of the reader the impression of the opposite being to the robust athletic figure with Thomsen's disease.

The juvenile or presenile cataract, which in 1911 *Greenfield* noted in a family with dystrophia myotonica, was by *Curschmann* (1912) added to *Steinert's* non-muscular organic dystrophies, and in 1913 *Grund* supplemented this picture with a description of mental defectiveness.

Because of the predominant role of the dystrophies in the pathological picture, *Curschmann* (1922) proposed the name dystrophia myotonica, which is now, especially in the Anglo-Saxon countries, the preferred designation

As mentioned, the familial occurrence of the disease was noticed at an early stage *Grund* (1913) was the first to find the disease in two consecutive generations, and in 1918 *Fleischer* established its regular familial occurrence

Curschmann's theory — that dystrophia myotonica and *Thomsen's* disease are clinically, as well as genetically, different — has been confirmed by many authors *Boe* (1932), however, found in two brothers pathological pictures, the one typical of Thomsen's disease and the other of dystrophia myotonica There are no reports of later investigations of these two brothers, which is unfortunate as the possibility of delayed manifestation of muscle dystrophy cannot be excluded

Boeters (1935), on the basis of unsatisfactory clinical investigations, thought that patients with dystrophia myotonica might occur in the same family as patients with Thomsen's disease, and *Maas & Paterson* (1939) arrived, partly by theoretical considerations, to the conclusion that Thomsen's disease, paramyotonia, and dystrophia myotonica are identical and in reality constitute variants of dystrophia myotonica My own investigations have as their special aim the further elucidation of this problem

Among the many theories on the ethiology of dystrophia myotonica, *Naegeli's* (1917) must be mentioned He found the pathological picture so dominated by the endocrine symptoms that, in his opinion, the ailment must be a heritable, endocrine disease of which the muscular symptoms were but one single part

To cover dystrophia myotonica, *Curschmann* (1912) applied *Erb's* statement on the ethiology of Thomsen's disease in a slightly altered form *Erb* wrote· "It is therefore conceivable that Thomsen's disease is a form of muscular trophoneurosis, the actual origin and seat of which must, consequently, be sought in the central trophic organs." Here *Curschmann* only wanted to alter "Thomsen's disease" to "dystrophia myotonica" and substitute "muscular trophoneurosis" for "trophoneurosis in muscles as well as in the endocrine system"

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Before embarking upon a further discussion on the ethiology of the disease, thorough pathologico-anatomic investigations must be available. Up to the present moment surprisingly few such investigations have been published, and the especially histological investigations have yielded

such varied results that it has been impossible to form a clear picture to support a valid theory as to the ethiology of the disease.

During the last ten years dystrophia myotonica has been given an increasing amount of attention, especially in reports from Great Britain and the United States. Besides myotonia, special interest has been devoted to the variegated clinical picture (*Ravin & co-workers*), and to the heredobiologic aspect [*Boeters* (1935) and *Maas & Paterson* (1943)].

B. SYMPTOMATOLOGY

Steinert's and *Curschmann's* classic descriptions of the symptomatology in dystrophia myotonica has, since their appearance, been confirmed and further augmented by a long series of casuistic and a few fuller reports. [*Rohrer* (1916), *Adie & Greenfield* (1923), *Rouquès* (1931), *Maas* (1937), and *Waring, Ravin & Walker* (1940)].

Whereas the symptoms in Thomsen's disease are distinctly muscular with myotonia and possibly muscle hypertrophy, the clinical picture in dystrophia myotonica is extremely varied. Apart from the myotonia, which characterizes the disease, there is found more or less pronounced muscle dystrophy with characteristic localization. To this picture must be added an almost kaleidoscopic collection of non-muscular dystrophies, and in examining these one touches a number of interesting pathophysiological problems

My own material comprises 101 living patients with dystrophia myotonica At the clinical investigations I have especially stressed the importance of the non-muscular organic dystrophies. The clinical descriptions have been supplemented by histological examinations of the endocrine organs of three patients who were subjected to autopsy.

Together with an investigation of the mental changes I have gone into the question of the effect of the disease on the social conditions of the patients That problem is certainly the most important for patients suffering from this incurable disease.

1. MYOTONIA

In Chapter II on *Myotonia*, this symptom has been described in detail and mention will here be made only of its special aspects with regard to dystrophia myotonica.

It must at once be stated that *Buchthal & Clemmesen* in 1941 investigated a number of patients from my material, and they arrived at

so with dystrophia myotonica. Up to now the earliest age of manifestation of myotonia in this disease has been reported by *Maas* (1937) in a child of three, who had mechanical myotonia. I have myself ascertained mechanical myotonia in a boy of two (157), who had active myotonia at the age of four. Besides I have found active myotonia in several children, aged between six and nine.

The age of manifestation, according to my patients and their relatives, varied between five and sixty, the average age being 18.6 years. Four old patients stated that their myotonia had become manifest between fifty-seven and sixty.

It is even more difficult to fix the time of manifestation with regard to the muscular dystrophies as they steal upon the patient and in the beginning are felt only as an inconsiderable reduction of strength.

As a rule, myotonia and muscle dystrophy become manifest more or less simultaneously, but in a few cases, e.g. as in two of my patients (Nos. 42 and 107), the myotonia can be demonstrated for several years before the dystrophy becomes manifest. Personally, I have never come across cases with reversed symptoms — muscle dystrophy without myotonia — but a number of authors have reported such cases of dystrophia myotonica sine myotonia. This phenomenon will receive later mention.

The *degree of myotonia* may diminish if the muscles in question become dystrophic, and it may be difficult to demonstrate the myotonia in severe cases. Both reported cases of dystrophia myotonica sine myotonia (*Curschmann* 1922 and *Amyot* 1938) were extremely severe, and there is a probability that the myotonia was impossible of demonstration on account of muscle dystrophy. The active myotonia was very indistinct in a number of my patients with severe dystrophy, but careful examinations invariably revealed myotonia to be present. In none of my cases have symptoms of myotonia been absent.

The *localization of myotonia* frequently differs from that of dystrophy. Thus, active myotonia is almost constantly found in the finger flexors, and mechanical myotonia can be demonstrated in the finger extensors, in the thenar and the edge of the tongue. Most often the dystrophies begin in the facial muscles and the sternocleidomastoid muscle, and thus myotonia and dystrophy in the initial stage are found in well separated muscle groups. Further, there is no proportion between the distribution of myotonia and dystrophy, as it frequently happens that the myotonia is very limited in cases where the dystrophy is widely spread.

Taken as a whole, myotonia and dystrophy seem to appear independently, although the symptoms become manifest about the same time.

As to the cause of myotonia in dystrophia myotonica, it has been discussed whether the myotonia might have any connexion with the

organic dystrophies of this disease. Since *Lundborg's* paper in 1904 — in which he propounded the theory that myotonia, like tetany, is caused by disturbances in the calcium metabolism — special attention has been focused on the parathyroid glands. But many fatal blows have struck the theory, the last directed in 1931 by *Rouquès* who went thoroughly into this problem. Nor does a connexion with dystrophy in other organs appear a probable solution, when it is borne in mind that the myotonic symptoms are the same as in Thomsen's disease where no dystrophic organic symptoms are found

Treatment of myotonia with quinine has been mentioned It has been tried in a number of cases of dystrophia myotonica in previously reported as well as in the present material — and with good effect when used during comparatively short periods The effect is upheld only so long as the quinine is administered. There have been no opportunities of ascertaining whether there is habituation in this, as is the case in Thomsen's. disease. Quinine treatment has been tried by several patients in this writer's material, but the treatment was only continued in two cases with dystrophia myotonica The treatment rarely helps these patients to become fit for working, because myotonia is never the primary cause of disablement Only in those few cases where the patient is still able-bodied, but hampered by myotonia, have I found reason to apply quinine The rest need money more than quinine

2 MUSCLE DYSTROPHY

Muscular dystrophy had been regarded as the more important dystrophic symptom until *Curschmann* (1912) directed the attention to the non-muscular organic dystrophies.

Muscular dystrophies affect only striated musculature, whereas the smooth musculature always remains unchanged

Dystrophies are not preceded by pains and not accompanied by fibrillation as are medullarily and neurogenously conditioned atrophies Most frequently they are fairly symmetrical, but in the initial stages one may generally find dystrophy in, e g. one of the sternocleidomastoid muscles

The characteristic localization of the muscle dystrophies is found in no other diseases with myatrophy of a neurogenous or muscular nature Especially specific is the dystrophy of the sternocleidomastoid muscle

The nature of the dystrophies and especially their relation to the other myatrophies have been elucidated by *Buchthal & Clemmesen* (1941) through the examination of some of my patients. The dystrophies were,

electromyographically, of the same character as in progressive muscular dystrophy and different in nature from neurogenous atrophies. Histologically *S. Wohlfahrt & G. Wohlfart* (1935) arrived at the same result.

Therefore, the dystrophies in dystrophia myotonica are likely to be of a peripheral, muscular nature.

Localization of Muscular Dystrophies.

Ocular Muscles.

The levator palpebrae superioris muscle is a frequent seat of dystrophy with resultant ptosis of upper eyelid. The ptosis is further increased by the almost constant enophthalmos. The other muscles never seem to be seriously affected, as the eye movements are always free.

Mastication Muscles.

The majority of patients present dystrophy of mastication muscles The temple regions are hollow, and the chin is pushed forward, mouth open, on account of the weak mastication muscles. *Rossolimo* (1902) reported habitual jaw dislocation which has been repeatedly described since then In my own material there are several patients with this infirmity.

Dystrophy of mastication muscles is one of the reasons why these patients are slow over eating.

Facial Muscles.

First and foremost the orbicularis oculi muscle is most often the seat of dystrophy. For this reason the patient suffers from lagophthalmos, a symptom noticed by the patient's relatives Further, the dystrophy affects most mimic muscles in forehead, cheeks, chin and mouth region. This gives the patient a flabby or gaping expression: the mouth is slightly open and the face practically devoid of mimics. This condition is termed myopathic facies. The facial expression is, however, different from that of other disease with myatrophy, as it is distinctly characteristic of dystrophia myotonica These patients from different families often resemble each other more than the members of their own families Patients with pronounced dystrophia myotonica can therefore be recognized from their face only. Thus, I have recognized four of my propositi from their myopathic facies (Figs. 8 and 9).

Pharynx, Larynx, and Esophagus.

Dystrophy in the muscles of these organs are found very frequently, and certainly in all severe cases of dystrophia myotonica. It causes difficulties in speech and swallowing

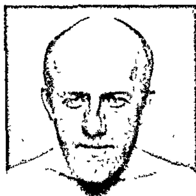


Fig 8



Fig 9

Dystrophia myotonica (patients Nos 53 and 160) Myopathic facies, frontoparietal baldness and flattened front side of neck





Fig 10

Dystrophia myotonica (patient No 44) Dystrophy of right sternocleidomastoid muscle

The *laryngeal muscles* may be the seat of dystrophy [*Steinert* (1909), *Fox* (1909), and *Lamby* (1931)]. *Steinert* found that the patients flung out the words by expiratory movements instead of using the glottis muscles, and autopsy revealed dystrophy in the interarytenoid muscles

Laryngoscopy was made on four of my patients. Only in one case was found deficient occlusion of the vocal folds, and a number of patients had hoarse, monotonous and weak voices, indicating dystrophy of the laryngeal muscles.

The *pharyngeal muscles* are very often the seat of dystrophy. *Albrecht* (1920) found dystrophy in the velum palatinum, shrivelled secretion on the throat wall, and foaming saliva in the piriform recess, indicating deficient functioning of the throat muscles

Swallowing difficulties and bulbar speech with nasal voice are very frequent symptoms of dystrophia myotonica, and I have in a number of cases observed dystrophy in the velum palatinum and dried-up throat secretion In the four cases submitted to examination by a laryngoscopist the patients had nasal speech, but the muscle dystrophy was, nevertheless, overlooked.

Like myopathic facies, the speech is characteristic of patients with dystrophia myotonica In almost all cases it is very rapid, not to say gabbling, the voice is monotonous, sometimes hoarse, weak and nasal Articulation is bad, rendering the speech extremely indistinct The bad articulation is due to dystrophy in tongue and facial muscles [*Albrecht* (1920) and *Lamby* (1931)].

The *musculature of the esophagus* may be the seat of dystrophy in the upper third, corresponding to the striated musculature. Three autopsies have given me opportunities of making this observation Clinically *Albrecht* (1920) reported slack walls and big lumen in the upper part of the esophagus, and by roentgen examinations *Terrien, Sainton & Veil* (1929), *Lamby* (1931), and *d'Antona* (1935) observed widening of the upper part of the esophagus

Two of my patients were subjected to such examination, but the passages found were normal

The dystrophic changes in the pharynx and the upper part of the esophagus may certainly cause difficulty in swallowing. Information on this point is obtained only by direct questions to the patients, as they are frequently too stupid to report it themselves. Some of my patients suffered from swallowing difficulties, but not to a degree so pronounced as to constitute a serious obstacle against the intake of food.

Tongue

Dystrophy in the tongue musculature is generally found only in severe cases It manifests itself by a furrowed or folded tongue surface and reduced volume. Observation has not been made of special consequent difficulties

Muscles of the Neck

The platysma myoides becomes dystrophic alongside with the facial muscles so that it may be completely absent in severe cases.

The muscle dystrophy most characteristic of the disease is that of the sternocleidomastoid muscle In lighter cases one of the muscles may be atrophic, and in more severe stages of the disease it is impossible to demonstrate the muscles, and the anterior side of the neck appears peculiarly flattened out (Figs 9 and 10)

In severe cases the muscles of the back of the neck may be dystrophic so that the characteristic prominence of the semispinalis capitis muscle is lacking

A result of dystrophy in the muscles of the neck is that the patient, when lying, is unable to raise his head from the pillow, but drops it backwards when attempting to sit up In order to avoid this unpleasant drop of the head, many of these patients must turn over on one side before raising the upper part of the body Dystrophy in the muscles of the back of the neck causes the head to droop forward perceptibly One of my patients with severe dystrophies in the muscles of the neck had to balance his head slightly backwards at a certain angle, or it would drop either forwards or backwards

Long Muscles of the Back

Dystrophy in these muscles may accentuate the natural curves to a considerable degree, making the back markedly curved — beginning with the projecting head and ending with the deep lumbar lordosis (Figs 11 and 12)

Abdominal Muscles and Diaphragm

Dystrophy in these muscles to a considerable degree adds to the aggravation of the patient's carriage The abdomen is slack and prominent without becoming completely paretic, however. Difficulties in evacuation and respiration are unknown, but coughing may be of a paralytic nature

Shoulder Muscles.

Even in lighter cases dystrophy of the supraspinatus and infras
muscles are frequently found In severe cases the deltoid musc
likewise be affected, disabling the patient to a serious degree. In
this writer's patients there was dystrophy of the lower part of the
muscle, while the upper part was prominent like a puff sleeve

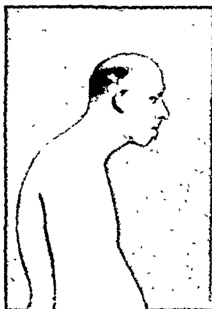


Fig 11

Dystrophia myotonica (Patient No 115) Frontoparietal baldness, myopathic facies, hanging jaw, drooping head and accentuated curvatures of the back

Upper Arm Muscles

Only in severe cases may dystrophy be found in these muscles
if so it will be of an extremely disabling effect because of its hamp
of the elbow movements Two of my patients had severe dystro
in these muscles and found it very difficult to carry the food to
mouths. Further, they were not themselves able to manage dressing
undressing. When walking, their arms hung slack like those of a

Forearm Muscles

Whereas the active myotonia is primarily localized to the finger
ors, dystrophy is generally first observed in the forearm extensors.

ten & Gibb (1909) and *Steinert* (1909) considered this localization typical and especially drew attention to dystrophy in the brachioradialis muscle. Also the flexors may become dystrophic in severe cases, with *resultant reduced strength in the fingers so that the patients may drop* objects they hold in their hands and not have the strength to use tools.

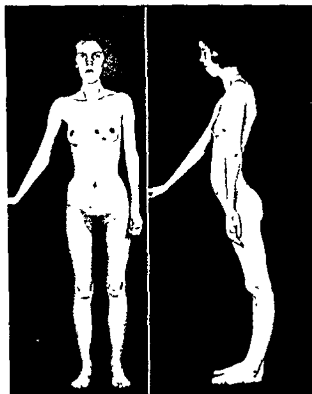


Fig 12

Dystrophia myotonica (Patient No 32) Emaciation myopathic facies deep-set eyes slack mammae, accentuated lumbar lordosis and recurvation of knees

Small Hand Muscles

Dystrophy in these muscles, and especially in the thenar, are often among the earliest of onset, but are, on the other hand, not nearly so frequent and regular as dystrophies in face, neck, and forearms

Severe cases may present dystrophy in the thenar as well as in the hypothenar muscles, but severe dystrophy is rarely observed in the interossei muscles.

Effect of these dystrophies: non-ability to perform adjusted movements of the fingers, e. g. rendering the patient unable to button his clothes, turn the key in a lock, or hold knives and forks in the usual way. In such cases the fingers are frequently somewhat unagile and stiff. Further, their movements may be somewhat hampered by the myotonia.

Hip Muscles

The hip muscles are but inconsiderably affected by dystrophia myotonica — in contradistinction to what is the case in progressive muscle dystrophy If the patient has severe and widely-spread muscle dystrophy, these muscles may be dystrophic, and the patient is severely disabled

Thigh Muscles

The quadriceps femoris muscle is not infrequently dystrophic. This fact causes the patient difficulties in getting up from a chair, and he easily falls Generally such patients walk with strong recurvation of the knees, *partly due to the simultaneous talipes equinus. In severe cases the dystro*phy may affect extensors as well as flexors These dystrophies disable patients to a considerable degree (Fig. 12)

Lower Leg Muscles.

Apart from the favourite sites previously mentioned, the muscle dystrophy is frequently localized to the anterolateral side of the lower leg. Less affected are, generally, the muscles of the back side Resultant of these dystrophies the patients acquire dropfoot. I spotted one of my propositi in the street because of his cock's gait and his typical myopathic face.

Feet Muscles.

No previous has been made of dystrophy in these muscles.

Besides dropfoot, one of my patients had clawfoot, which was undoubtedly due to dystrophy in the small muscles of the foot. He had to *have his footwear specially made.*

Sphincter Muscles

Previous reports invariably contain statements to the effect that no dystrophies have with certainty been observed in the external sphincter ani and the sphincter urethrae membranaceae None of my patients have complained of incontinence, but one had flatulent tendencies and a somewhat atonic external sphincter ani

Effect of Muscle Dystrophies on Working Ability.

In table 6 below the *degree of the dystrophies* is shown by figures 0 to 3. In estimating this degree special consideration has been given to the reduction in working ability, for which reason it has first and foremost been determined according to the muscle dystrophies of the extremities.

0. working ability not reduced on account of muscle dystrophy.
1. physical working ability reduced to a lesser degree.
2. physical working ability reduced to a considerable degree, so that the patient will have difficulties in performing manual work.
3. physical working ability reduced to a degree that makes it impossible for the patients to perform manual work, they will, therefore, generally be invalids in the meaning of the law (i e working ability less than 33⅓ per cent)

The degree of muscle dystrophy in this writer's 101 living patients appears from the following table:

Table 6

101 patients with dystrophia myotonica	Degree of muscle dystrophy			
	0	1	2	3
Between ages 15 and 60	16	34	20	15
Ages under 15 and over 60	10	2	1	0
Total	26	36	21	15

3 CREATINE AND CREATININE METABOLISM

In certain patients with atrophy in the muscles there may be found abnormal creatine-creatinine excretion in the urine.

In normal persons there is physiological creatinuria during the whole period of childhood In women there is frequently intermittent, moderate creatinuria in connexion with menstruation, whereas in adult men there is, generally, no creatine excretion in the urine [*Nevin* (1934)]

During infectious diseases, thyrotoxicosis, carcinomatosis, cardiac insufficiency etc and in patients with muscular rheumatism there may be found creatinuria to varying degrees [*Brochner-Mortensen & Clemmesen* (1941)].

Pathological creatinuria is found to be especially pronounced in patients with progressive muscular dystrophy, but may be demonstrated

in varying degrees in other diseases with musle atrophy [*Kostakow & Slauck* (1933)]

No pathological creatinuria has been found in patients with Thomsen's disease [*Rosenbloom & Benson* (1914), *Milhorat & Wolff* (1936), *Poncher & Wade* (1938), and *Eichler & Hattingberg* (1938)].

Only in a few cases of dystrophia myotonica (4) has there been demonstrated pathological creatinuria [*Morgulis & Young* (1931) and *d'Antona* (1934)], but in the majority of patients investigated (17) the creatine excretion was very insignificant or moderate [*Burger* (1919), *Meyer* (1920), *Kostakow & Slauck* (1933), *Adams, Power & Boothby* (1935), *Kolb, Harvey & Whitehill* (1938), *Milhorat & Wolff* (1938), and *Lindsley & Curnen* (1938)] The creatinuria was neither so constant, no so clear as in progressive muscular dystrophy

Nor is the creatinine excretion certain to have undergone changes in patients with dystrophia myotonica Varying creatinine coefficients (mg. of creatinine in 24 hours' urine divided by body weight in kg.) have been found, but in most cases the figures were below normal [*Burger* (1919), *Adams, Power & Boothby* (1935), *Milhorat & Wolff* (1938), and *Lewis, Ravin & Lewis* (1941)].

Creatine tolerance tests have been made on a number of patients with dystrophia myotonica. The results were extremely varying and without any definite tendency [*Morgulis & Young* (1931), *Kolb, Harvey & Whitehill* (1938), and *Milhorat & Wolff* (1938)].

The administration of glycine during protracted periods to patients with progressive muscular dystrophy frequently results in considerable rise in the creatine excretion for the first two or three weeks, followed, generally, by a considerable decrease, so that the creatinuria finally may be lower than before the treatment This rise and fall has been ascertained in three patients with dystrophia myotonica [*d'Antona* (1934) and *Lewis, Ravin & Lewis* (1941)], but otherwise there has been but slight or no increase resultant from the administration of glycine [*Kostakow & Slauck* (1933), *Adams, Power & Boothby* (1935), and *Milhorat & Wolff* (1938)].

Own Investigations.

In this writer's material creatine-creatinine examination of the urine has been made only in three cases of dystrophia myotonica

No	Sex	Age	Weight	Creatine	Creatinine
32	F	18	38 kg	0—150 mg	544—756 mg
86	I	41	43 kg	272—275 mg	900—921 mg
181	M	46	79 kg	38— 56 mg	

No 86 received glycine treatment alongside with desoxycorticosterone acetate. After three weeks treatment the creatinuria had risen from 275 to only 330 mg The creatinine excretion rose from 900 to 1050 mg.

Thus, the results of these few experiments fall well in line with the previous descriptions

Summary

Changes of the creatine-creatinine excretion in the urine of patients with dystrophia myotonica is by no means so considerable as in progressive muscular dystrophy, and as a rule the changes are completely uncharacteristic

4 REFLEXES AND SENSIBILITY

The *tendon reflexes* are frequently weakened in patients with dystrophia myotonica, and at times they may be impossible of demonstration The cutaneous reflexes, on the other hand, are generally normal [*Wilson* (1940)]

Steinert (1909, at a histological examination of the spinal cord of a patient with areflexia in the legs, found degeneration of the posterior funiculi Later investigations have, however, revealed that this feature does not belong to the pathological picture of dystrophia myotonica It is likely that the patient, besides the muscle disease, has had luetic locomotor ataxia.

As a rule *sensibility* is unchanged A few authors have observed slight hypesthesia and hypalgesia peripherally in arms and legs [*Rossolimo* (1902), *Pelz* (1907), *Rohrer* (1916), *Curschmann* (1936), and *Maas* (1938)] *Maas* further made the interesting observation that the sensitivity to vibration is reduced in patients with dystrophia myotonica He applied an electrical vibrator with a frequency of 300/sec and with a possibility of increasing the vibrations In this manner he was able to determine an absolute threshold, and comparing a number of normal persons with patients with dystrophia myotonica he found considerably higher thresholds in the latter group

Own Investigations

The tendon reflexes were examined in 39 of this writer s patients with the following results

Reflexes	Normal	Weakened	Absent
Biceps and triceps brachii	7	12	20
Patellar	22	14	3
Achilles tendon	21	12	6

It appears that the tendon reflexes are most frequently weakened in the arms. In the 20 patients without biceps and triceps reflexes the degree of muscle dystrophy averaged 2 0, so that the reduced reflexes are mainly found in patients with severe muscle dystrophy. There were however a number of patients with but slight or no dystrophy at all in the muscles of the arms, and in them it was impossible to produce tendon reflexes (Nos. 44, 56, 103, 122, 155, 166). This would show that the reduced tendon reflexes are not definitely bound up with the muscle dystrophy.

Sensibility to touch and pain as well as the joint sense was normal in the 19 patients investigated. In No 181 there was, however, doubtful hypalgesia distally in the extremities. The reaction to vibrations was investigated only with a big tuning fork, and in this manner it was impossible to demonstrate any abnormalities in 4 patients.

Summary.

The tendon reflexes are frequently reduced — especially in patients with severe muscle dystrophy The reflexes may well be reduced in cases where the muscles in question are not dystrophic.

The sensibility, as a rule, remains unchanged A few authors have described cases of slightly reduced sensibility distally in the extremities, and *Maas* has demonstrated that the reaction to vibrations is often reduced in patients with dystrophia myotonica.

5. NON-MUSCULAR DYSTROPHIES

Steinert (1909) was first to realize that dystrophia myotonica is not a purely muscular disease Besides the characteristic muscle dystrophies, he found in his patients symptoms of dystrophy in other organs· testes, struma, frontal alopecia, and acrocyanosis. In his conception, these symptoms ranked alongside with the muscular dystrophies.

Greenfield (1911) augmented the description of the non-muscular dystrophies by the demonstration of cataract as an important symptom, and *Curschmann* (1912 and 1915) in an excellent manner outlined the varied complex of symptoms and called the disease dystrophia myotonica, by the order of these two words he wanted to stress the dystrophic symptoms as being more important than the myotonia. These reports roused in other authors an interest in the disease, and especially in the non-muscular dystrophies. These dystrophies, and especially the endocrine changes, have been the subject of growing attention in the many reports that have by now appeared.

The non-muscular dystrophies are localized in a number of various organs, and the complete pathological picture with myotonia, muscular and non-muscular dystrophies, is extremely varied.

The following chapters will contain descriptions of the dystrophic changes, outside the striated musculature, observed and reported up to the present time, and attempts will be made at going further into the interesting problems attached to these observations. The great question concerning a possible common cause of the muscular and non-muscular changes will not be further dealt with: as long as reliable histological investigations of the C. N. S. are not available, a discussion of this important point is futile.

I have made pathologico-anatomic examinations of three patients on whom histological reports will be given in connexion with the treatment of dystrophic changes in the endocrine organs. It is my hope that I shall later, together with *Larus Einarsson*, be able to publish a satisfactory histological description of muscles, peripheral nerves and the C. N. S.

Of the non-muscular dystrophies I shall first deal with *cataract*. In the majority of patients there are more or less pronounced cataractous changes of a comparatively characteristic nature. The symptom may appear as an isolated phenomenon in families with dystrophia myotonica, and the disease may be inherited through family members who have no other symptoms but cataract.

Other eye symptoms in dystrophia myotonica — as blepharoconjunctivitis and lagophthalmos — are more likely to be related to the muscular dystrophies.

Dystrophic changes may, generally, be demonstrated in several of the *endocrine glands*. First described of these endocrine dystrophies was the gonadal dystrophy which is almost invariably found, more or less pronounced, in adult patients. Further there seems to be dystrophy of the thyroid gland, apparent from reduced B. M. R. Dystrophy in the internally secreting gland tissue of the pancreas has never been ascertained with certainty, but may nevertheless be present to a slight degree. Corti-adrenal dystrophy may be the cause of the frequent muscular asthenia that hampers the already dystrophic muscles. The parathyroid glands have never displayed clear signs of dystrophy. Finally there are certain symptoms which may support the theory of dystrophic changes in the hypothalamus-hypophysis system.

Alopecia of the frontal type is especially pronounced in men, together with myopathic facies, produced by muscle dystrophy, it endows the patient with a typical appearance. Its cause is unknown.

Acrocyanosis is a very frequent symptom, which is most likely due to dystrophic changes in the vegetative centres concerned with the regulation of the vascular system.

Cardiac changes very rarely become manifest, but in a number of cases electrocardiographic changes may be demonstrated.

But of all the non-muscular dystrophies, the *mental changes* may be characterized as extremely prominent in importance. Firstly, there is deficiency of intelligence, which may be severe to a degree requiring the term: mental deficiency, and, secondly, there is more or less evident reduction of initiative, which may be so serious that the patient is unfit for work. Despite their miserable condition and generally deteriorated circumstances, most of the patients are almost morbidly satisfied and self-overestimating.

The working ability, reduced by the muscular dystrophies, is further deteriorated by the non-muscular dystrophic changes — and especially those of a mental nature. The present investigation will reveal that about two thirds of the patients are disabled to a degree that prevents them from managing without aid.

CATARACT IN DYSTROPHIA MYOTONICA

Cataract takes up a special position among the symptoms in dystrophia myotonica, because lenticular opacities may be the only symptom of the genotype. It is found in almost all patients with muscular symptoms and in a number of their apparently healthy relatives. The morphology and localization of the opacities are ordinarily so characteristic that a special designation — cataract in myotonia — is brought into use.

Greenfield (1911) was the first who realized that cataract is a symptom in dystrophia myotonica and that it may appear also in other healthy family members during several [illegible]

B[illegible] e and [illegible] [chan]ges he found in four pati[ents with myo]tonia and muscle dystrophy were due to latent tetany. He found dust-like opacities with a tendency to melt together into streaks and lines in the anterior cortex besides star-shaped cataract in the posterior cortex. *Greenfield's* description is in close correspondence with this, as he in particular found polar star-shaped cataract in the posterior cortex.

Fleischer (1916, 1917, 1918, and 1922) and his chief at the eye clinic at Tubingen, Germany, had during several years noticed that a number of the patients with presenile and juvenile cataractous changes looked miserable and had a characteristic facial expression, but they did not become aware of dystrophia myotonica until they read *Curschmann's* report of 1912. *Fleischer's* description of the lenticular opacities in all essentials corresponds to *Bartels's* polar, posterior cortical star-shaped

cataract. Besides there were, however, generally some white, point-shaped, shining cortical opacities *Fleischer* found that the cataract was progressively inherited through several generations, which feature has also been reported in other types of hereditary cataract.

Slit lamp examination was introduced in 1911, but not until about 1920 was it brought into general use on patients with dystrophia myotonica.

Vogt (1921, 1922, 1924, and 1931) has described and depicted the view by slit lamp examination in dystrophia myotonica He thought that the coarser lenticular opacities described up to then were not especially typical of that disease, as it was possible to find similar polar, cortical opacities in complicated cataract On the other hand he was of the opinion that the first fine lenticular opacities were more characteristic and that at this stage of development it was more justified to talk of specific cataract in myotonia

The opacities are, as in certain other forms of cataract, localized cortically with a free, subcapsular zone, and angular shining, white or coloured, fine opacities are characteristics of beginning cataract in myotonia. As a rule the opacities are especially present in the posterior cortex

In more advanced cataract in myotonia the opacities in the cortex are less characteristic with augmented nuclear sclerosis, porous, limestone-like, centrally located opacities, or condensation of dust- or point-like opacities along the suture lines with a tendency to stellate formation Simultaneous appearance of cortical, white, shining, or coloured grains may support the suspicion of cataract in myotonia This stage of development corresponds to *Fleischer's* description of cataract in myotonia The mature cataract in myotonia was described by *Vogt* (1931) as being cloud-like, as opposed to the more dense cataract in tetany

This description of the slit lamp picture of cataract in myotonia has in all essentials been confirmed by a great number of authors [*Scheffel* (1925), *Isakowitz* (1926), *Goulden* (1928), *Gifford, Bennet & Fairschild* (1929), *Caughey* (1933), *Maas* (1937), *Kolb, Harvey & Whitehill* (1938), *Allen & Barer* (1940), and *Sautter* (1941)], whereas for example *Waring, Ravin & Walker* (1940) were of the opinion that it was not correct to speak of a specific cataract in myotonia

It may prove difficult to distinguish cataract in myotonia from that of tetany, as the opacities are similar in localization and appearance. In cataract in tetany there is frequently fine, thread-formed, possibly bent opacities more deeply located in the cortex, and the above-mentioned mixture of white, shining, and coloured opacities, as described by *Vogt* in cataract in myotonia, are not typical of cataract in tetany *Knüsel* (1924), *Gronholm* (1927), and *Meesmann* (1938), who associated myotonia with tetany, thought that cataract in myotonia was identical with

that of tetany. However, it has been established for long that myotonia has nothing to do with tetany, and that lenticular opacities are a dystrophic symptom [*Rouquès* (1931)]

In certain cases of myxedema and Mongolian idiocy, juvenile lenticular opacities, similar to those of dystrophia myotonica, may be demonstrated. Like the latter, they are mainly found in the cortex and may be white, shining and coloured. *Goulden* (1928) and *Rivoire* (1930) supposed that these opacities were caused by disturbances in the internal secretion.

Finally it must be mentioned that normal lenses may display single grain-shaped or dust-like opacities without characteristic localization [*Pellaton* (1924) and *Vogt* (1931)]

Vogt (1922) considered cataract in myotonia to be a constant symptom in patients with dystrophia myotonica, and *Allen & Barer* (1940) and *Sautter* (1941) found lenticular opacities in all their patients (Nos. 22 and 24, respectively). *Maas* (1937) found the lenticular opacities to be absent in certain cases although other symptoms of dystrophia myotonica were clearly present, *Vos* (1936) found lenticular opacities in 23 of 28 patients.

The earliest ages of manifestation of cataract in myotonia were stated by *Fleischer* (1918) and by *Vos* (1936) to be between the ages of 20 and 35, and between 10 and 20, respectively *Sautter* (1941) thought that the first opacities appeared towards the later 'teens and that hereafter they slowly increased in number, generally not affecting the vision until after forty. In his investigations he was unable to find any immediate connexion between the degree of development of the cataracts and of the other symptoms, and several descriptions exist of manifest cataract with but weak muscular symptoms [*Vogt* (1931) and *Maas* (1937]. *Vogt* imagined the possibility that patients with cataract in myotonia, but without other ascertained symptoms, might, nevertheless, have muscular symptoms to a very slight degree. The familial appearance of cataract in myotonia in otherwise healthy relatives of patients with dystrophia myotonica was first described by *Greenfield* (1911) and has later been repeatedly confirmed, *inter alia* by the heredobiological investigations made by *Fleischer* (1918) and by *Frey* (1925) It appears from their pedigrees that persons with cataract are genetic carriers, as among their descendants there are frequently patients with dystrophia myotonica. Such carriers are dangerous, because their fertility is not reduced. In his family investigations *Fleischer* found anteposition· many members of the first generation had senile cataract, in the second presenile cataract, and in the third generation dystrophia myotonica with juvenile cataract. This was *Fleischer's* basis for his theory of progressive heredity.

Vogt (1931) and *Bing* (1938) found increased cholesterol contents in

lenses of patients with cataract in myotonia, and they thought that the opacities were crystallized cholesterol precipitations. *Waring, Ravin & Walker* (1940) were unable to confirm this point, because they found normal cholesterol content in a lens with cataract in myotonia

Histological examination has been made by *Bielschowsky, Maas & Ostertag* (1933), who in the interstices between the lamellae found small dust-like, crystalline grains with lipoid reaction. *Sautter* (1941) found the nucleus intact and in the anterior cortex several small cavities, which were especially numerous in the equatorial zone. There was wasting of *the fibres in the posterior cortex He did not succeed in ascertaining* whether the crystalline precipitations in the cavities consisted of cholesterol

There are no special problems connected with the treatment of mature cataracts in myotonia [*Sautter* (1941)]

Own Investigations

As far as possible I have, in the family investigations, examined all persons with regard to manifest cataract were they able to read? and were there any macroscopically visible signs of cataract? In a number of cases the patients have been subjected to ophthalmoscopy

The investigation covers 874 living persons in 21 families with dystrophia myotonica. Of these, 101 had muscular and non-muscular symptoms, and 17 of these patients had manifest cataract. Of the remaining 773 persons, 12 had manifest cataract

Slit lamp examinations have been made on as many patients as possible and on a number of family members without symptoms of dystrophia myotonica. The examinations were made either at the hospitals where the patients had been admitted (the Kommunehospital, the Rigshospital, and the Militærhospital), or on out-patients at a number of practising ophthalmologists' and at the Eye Department of the Kommunehospital. All examinations have been made in mydriasis, which is necessary for demonstration of the fine changes.

The vision was more or less reduced in patients with coarser lenticular opacities, *but in the majority of patients there was no considerable reduction* of vision Nor have ophthalmoscopical examinations revealed any abnormalities beyond *lenticular* opacities

Slit lamp examinations were made on 47 patients, as well as on 21 family members without symptoms of dystrophia myotonica

These 21 family members were not picked at random, but were preferably very near relatives of patients. Manifest cataract was found in 5 cases (Nos. 141, 142, 119, 173 and 38) Six others (Nos 4, 8, 39, 43, 65, and 92) had lenticular opacities as found in patients with dystrophia myo-

tonica. In the pedigrees they have therefore been registered as having cataract in myotonia.

Finally, 7 other family members, not examined by slit lamp (Nos. 3, 49, 99, 150, 153, 154, and 158), had manifest cataract without other symptoms.

Of the 47 examined patients, 41 — or 87 per cent — had more or less pronounced lenticular opacities.

Manifest cataract in one or in both eyes was found in 6 patients (Nos. 54, 55, 67, 85, 120, and 146), in a number of cases the cataract had been operated on. As has been stated, a further 11 patients, not examined by slit lamp, had manifest cataract (Nos. 5, 36, 50, 76, 101, 126, 127, 128, 159, 168, and 179) These 17 patients were between 33 and 67 years and had an average degree of muscle dystrophy of 1.5.

In 18 patients (Nos. 15, 19, 26, 28, 42, 44, 53, 56, 62, 63, 64, 86, 117, 122, 149, 152, 164, and 175) between 19 and 56 years (34 years) and with muscle dystrophy 1.6, were found comparatively coarse lenticular opacities — corresponding to *Fleischer's* description — with cortical, rosette-shaped dimness and grain-formed crystalline opacities. Generally the opacities were most pronounced posteriorally, and the nucleus was always clear.

17 patients (Nos. 10, 13, 16, 24, 32, 37, 41, 45, 57, 69, 70, 91, 95, 103, 121, 165, and 181) between 14 and 46 years (32 years) and with muscle dystrophy 1.2, had comparatively fine and few opacities. In some cases the slit lamp picture corresponded to *Vogt's* description fine, crystalline, white or coloured cortical opacities, whereas in other cases there were less characteristic, finely spotted or larger, round opacities. The opacities were especially evident in the posterior cortex.

Finally there were 6 patients without lenticular opacities at slit lamp examination, aged between 11 and 49 (average age 25), and with an average degree of muscle dystrophy of 1.3.

From this appears, as might be expected, that the most developed lenticular opacities are found in the oldest patients, but there is no clear relation between muscle dystrophy and lenticular opacity — manifest cataract may be found in several older patients with very weak muscular symptoms (Nos. 76, 126, 127, 146, and 168), and on the other hand it may be impossible to demonstrate lenticular opacities in patients with severe muscle symptoms and dystrophies (Nos. 82, 93, and 97).

In 2 patients (Nos. 19 and 28) there were no opacities at the first examination, but fine opacities at an examination some years later. Already at the first examination these patients had severe muscle symptoms. It is not possible to give any definite age of the first manifestation of the lenticular opacities, but there were, in my material, no clear opacities in patients under 14.

In the 21 families investigated there were remarkably weak lenticular opacities in six (family No 2, 3, 8, 9, 10, and 18). In six other families (Nos. 1, 4, 5, 6, 7, and 13) the opacities were much more strongly developed. This fact points towards a familal disposition to lenticular opacities, independent of the other symptoms.

Two family members with lenticular opacities, but without muscular symptoms or non-muscular dystrophies (Nos. 38 and 43) were examined by electromyography for latent myotonia There was no prolonged electrical activity after voluntary innervation, nor after percussion near the site of the electrodes, and intravenous injections of 1 mg prostigmine produced no myotonic reaction

Among the deceased family members eighteen had had symptoms of manifest cataract, and in five there have possibly been muscular symptoms of dystrophia myotonica besides The possibility cannot be excluded that a number of these persons might have had senile cataract unrelated to dystrophia myotonica.

By investigating the living members of four families, it has been possible for me to confirm the heredity of cataract with apparent progression through several generations

In family No 1 patient No 3 had had presenile cataract, which had been operated on His daughter was a typical case of dystrophia myotonica, but without manifest cataract No 4 had typical, comparatively fine lenticular opacities (s I e) His eldest daughter had rather coarser lenticular opacities while four younger children had typical dystrophia myotonica with lenticular opacities The eldest daughter had several children with fully developed clinical pictures and lenticular opacities

In family No 4 two brothers had typical myotonic cataract one of them operated on The elder brother had two sons one of whom had dystrophia myotonica with lenticular opacities, the other with but fine opacities The younger brother had three children, two of whom were typical cases of dystrophia myotonica with fine lenticular opacities

In family No 5 one father had manifest cataract and his daughter dystrophia myotonica with incipient cataract

In family No 12 the mother of the propositus had senile nucleoid cataract at the age of 80 The propositus had severe dystrophia myotonica with cataract in myotonia, and all his four children have dystrophia myotonica one with a mature cataract in myotonia and two with evident lenticular opacities The youngest is a minor and has not been examined The eldest son has three children of whom two already present complete clinical pictures

It has not been possible for this writer to investigate further into the problem of whether this seeming progression is apparent or real. This would require a number of consecutive, completely investigated generations Possibly the progression appears by elective selection, since it is patients with cataract, but without other symptoms, who mainly propagate the family

tonica In the pedigrees they have therefore been registered as having cataract in myotonia.

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By investigating the living members of four families, it has been possible for me to confirm the heredity of cataract with apparent progression through several generations.

In family No 1 patient No 3 had had presenile cataract, which had been operated on His daughter was a typical case of dystrophia myotonica, but without manifest cataract No 4 had typical, comparatively fine lenticular opacities (s 1 e) His eldest daughter had rather coarser lenticular opacities while four younger children had typical dystrophia myotonica with lenticular opacities The eldest daughter had several children with fully developed clinical pictures and lenticular opacities

In family No 4, two brothers had typical myotonic cataract, one of them operated on The elder brother had two sons, one of whom had dystrophia myotonica with lenticular opacities, the other with but fine opacities The younger brother had three children, two of whom were typical cases of dystrophia myotonica with fine lenticular opacities

In family No 5 one father had manifest cataract and his daughter dystrophia myotonica with incipient cataract

In family No 12 the mother of the propositus had senile nucleoid cataract at the age of 80 The propositus had severe dystrophia myotonica with cataract in myotonia, and all his four children have dystrophia myotonica — one with a mature cataract in myotonia, and two with evident lenticular opacities The youngest is a minor and has not been examined The eldest son has three children, of whom two already present complete clinical pictures

It has not been possible for this writer to investigate further into the problem of whether this seeming progression is apparent or real This would require a number of consecutive, completely investigated generations. Possibly the progression appears by elective selection, since it is patients with cataract, but without other symptoms, who mainly propagate the family

tonica. In the pedigrees they have therefore been registered as having cataract in myotonia

Finally, 7 other family members, not examined by slit lamp (Nos. 3, 49, 99, 150, 153, 154, and 158), had manifest cataract without other symptoms.

Of the 47 examined patients, 41 — or 87 per cent — had more or less pronounced lenticular opacities.

Manifest cataract in one or in both eyes was found in 6 patients (Nos. 54, 55, 67, 85, 120, and 146); in a number of cases the cataract had been operated on. As has been stated, a further 11 patients, not examined by slit lamp, had manifest cataract (Nos. 5, 36, 50, 76, 101, 126, 127, 128, 159, 168, and 179) These 17 patients were between 33 and 67 years and had an average degree of muscle dystrophy of 1.5.

In 18 patients (Nos 15, 19, 26, 28, 42, 44, 53, 56, 62, 63, 64, 86, 117, 122, 149, 152, 164, and 175) between 19 and 56 years (34 years) and with muscle dystrophy 1.6, were found comparatively coarse lenticular opacities — corresponding to *Fleischer's* description — with cortical, rosette-shaped dimness and grain-formed crystalline opacities. Generally the opacities were most pronounced posteriorally, and the nucleus was always clear.

17 patients (Nos. 10, 13, 16, 24, 32, 37, 41, 45, 57, 69, 70, 91, 95, 103, 121, 165, and 181) between 14 and 46 years (32 years) and with muscle dystrophy 1.2, had comparatively fine and few opacities. In some cases the slit lamp picture corresponded to *Vogt's* description: fine, crystalline, white or coloured cortical opacities, whereas in other cases there were less characteristic, finely spotted or larger, round opacities The opacities were especially evident in the posterior cortex.

Finally there were 6 patients without lenticular opacities at slit lamp examination, aged between 11 and 49 (average age 25), and with an average degree of muscle dystrophy of 1.3.

From this appears, as might be expected, that the most developed lenticular opacities are found in the oldest patients; but there is no clear relation between muscle dystrophy and lenticular opacity — manifest cataract may be found in several older patients with very weak muscular symptoms (Nos. 76, 126, 127, 146, and 168), and on the other hand it may be impossible to demonstrate lenticular opacities in patients with severe muscle symptoms and dystrophies (Nos. 82, 93, and 97).

In 2 patients (Nos. 19 and 28) there were no opacities at the first examination, but fine opacities at an examination some years later. Already at the first examination these patients had severe muscle symptoms. It is not possible to give any definite age of the first manifestation of the lenticular opacities, but there were, in my material, no clear opacities in patients under 14.

OTHER EYE SYMPTOMS IN DYSTROPHIA M

In connexion with the description of cataract in dystro
it is my intention to deal with a number of less serious
which have not received great attention up to now.

A number of my patients with dystrophia myotonica
thalmos, and when questioning the family it often turns
symptom has prevailed since childhood The symptom is cau
ness in the orbicularis oculi, which also results in reduced
ility The frequently appearing *blepharoconjunctivitis* must
viewed in this connexion, the symptom was described by *W*
& *Walker* (1940), who noticed it in nine out of thirteen pa
(1925), *Lemierre, Garcin & Laplane* 1932), and *Allen & B*
found the symptom in a number of patients, but other authors
it very little attention

At the examinations of my patients I have, like the ophtha
who performed the eye examinations, not been sufficiently con
this symptom to be able to state in figures its frequency. It is,
found very often, and as a result many patients have red-rimm
The wife of one of my patients noticed that her husband had th
rimmed eyes when especially weak and tired, and that the sy
diminished when he felt better Thus, the blepharoconjunctivi
appeared upon treatment with desoxycorticosterone acetate while
same time the patient's general muscle strength increased

As opposed to a number of previous authors [*Ortleb* (1912), *H*
mann (1916 and 1918), and *Amyot* (1938)] I have not found any
siderable increase of lacrimal secretion, but the eyes in a number of
ents with blepharoconjunctivitis are somewhat moist

Ptosis is an almost constant — more or less pronounced — sympt
due to weakness of the levator palpebrae superioris muscle There is
definite relation between the ptosis and the enophthalmos, although
latter aggravates the symptom One of my patients, an artist, had ptos
to such a severe degree that in order to be able to see he had to prop u
his eyelids with bits of matches The ptosis endows the patients wit
the typical, sleepy appearance

In previous descriptions of dystrophia myotonica *enophthalmos* had
received but passing mention [*Bielschowsky, Maas & Ostertag* (1933)
and *Amyot* (1938)], despite its being a frequent symptom Previously
published illustrations of such patients will recall the picture of their
deep-set eyes, and in the greater part of my patients, enophthalmos, re-
corded as "deep-set eyes," is an almost invariable symptom (Fig. 13).
In particular I have found the symptom in some patients who h
slight degrees of muscle dystrophy and were norm

Summary.

In the majority of patients with dystrophia myotonica are found lenticular opacities (in this writer's material 87 per cent).

Manifest cataract was found in 17 of my 101 patients. Average age: 50 years.

Slit lamp examination reveals, in the initial stage, cortical, spotted, frequently crystalline, white, shining, or coloured opacities. Generally there is a fine, subcapsular free region, and the majority of the opacities in the posterior cortex. The finest opacities were found in slightly less than half of my patients, but they were not quite so typical as described by *Vogt* (1931).

In older patients may be demonstrated coarser, less characteristic opacities in the cortex.

There are frequently augmented nuclear scleroses and condensation, in stellate formations, of dust- and point-formed opacities along the suture lines, or of a more porous, limestone-like central nature. As typical of cataract in myotonia are generally found cortical, white or coloured crystalline opacities [*Fleischer* (1918)]. These coarser opacities were found in about half of my patients.

The mature cataract in myotonia cannot with certainty be distinguished from other cataracts, but the nuclear opacities may, however, be described as more cloud-like than for example in cataract in tetany

There is no clear relation in development between cataract in myotonia and the other symptoms, and in the families the cataract may appear as the only symptom in parents and siblings, but not in children of the patients.

It is impossible to lay down the law as to the earliest age af manifestation of this symptom, but in my material no lenticular opacities were found in patients under 14. The opacities increase with the years, but the vision is rarely reduced until about the age of 40.

Judging from my investigations there may be familial disposition to cataract in myotonia.

It may be difficult to distinguish between cataract in myotonia, on the one hand, and cataract in tetany and lenticular opacities in myxedema and Mongolian idiocy on the other, but according to *Vogt* the crystalline, white or coloured opacities in the cortex as well as the free subcapsular region are quite characteristic of cataract in myotonia

Cataract in myotonia is dominant and, apparently, progressive of heredity. The questions of heredity will receive later mention.

bolic rate, and more or less pronounced colloidal and fibrotic thyroid gland. So, there seems to be some justification for the theory that enophthalmos in these patients is caused by dysfunction of the pituitary gland or higher vegetative centres.

DYSTROPHY OF ENDOCRINE GLANDS

GONADS — IN MALES

The earlier reports on patients with so-called myotonia atrophica contained descriptions of two patients with testicular atrophy [*Gaup* (1900) and *Furnrohr* (1907)], but it was *Steinert* (1909) who described atrophy of testes as a symptom of dystrophia myotonica The symptom was present in four of his six male patients, and these four were deprived of their former normal sexual potency

Curschmann (1912) confirmed this observation, as three of his six patients had testicular atrophy *Rohrer* (1916) in his bibliographical survey found that sixteen out of twenty-four had atrophy of testes and possibly simultaneously of the external genitalia. Nineteen male patients with dystrophia myotonica had been interrogated with regard to sexual libido, which appeared to be absent in seventeen cases *Maas* (1937) found that many patients, both with severe and light muscle symptoms, had small and soft testes and potency disturbances In cases of pronounced atrophy of testes the secondary sex characters were feebly developed A few patients, however, had retained the potentia generandi up to the ages of between thirty and forty

There has been published a number of histological examinations of atrophic testes from patients subjected to autopsy [*Hitzenberger* (1920), *Weil & Keschner* (1927), *Guillain, Bertrand & Rouquès* (1932) *Bielschowsky, Maas & Ostertag* (1933), and *Keschner & Davison* (1933)], and all these writers found atrophy of the epithelium of the convoluted tubules which had been converted into hyaline chords Apart from *Hitzenberger* (1920) and *Guillain, Bertrand & Rouquès* (1932), all the authors found hyperplasia in the interstitial tissue and especially of cells resembling the interstitial cells normally present

Attempts at substitution therapy were first made by *Slauck* (1933) together with *Kostakow* They investigated the effect of glycine and testiculin on the creatine excretion and muscle dystrophy, and thought they observed a definite effect *Hesser, Langworthy & Vest* (1940) treated four patients with testosterone propionate, 25 mg every other day for more than two months, and two of the cases with testicular atrophy obtained improvement, subjectively as well as objectively, whereas there was no definite effect on the other two patients without testicular atrophy.

in several fat patients, so it follows that the symptom is not caused by muscle dystrophy or malnutrition. I have made no exophthalmometric measurements (Hertel), but confined myself to general observation



Fig 13

Dystrophia myotonica (patient No 28) Myopathic facies and enophthalmos

The cause of enophthalmos in these patients is unknown to me, but it may be that it is due to dysfunction or dystrophy in certain endocrine glands, in particular the pituitary gland.

Bardram (1944) has published an exhaustive bibliographical survey of progressive exophthalmos from which appears that it is likely to be caused by hyperfunctioning of the pituitary gland, or, possibly, by higher centres in the diencephalon related to the functioning of the thyroid gland It has been discussed whether the thyrotropic hormone might be the agent, but other writers have maintained that the cause of exophthalmos must be sought in another special hormone fraction.

Albert (1945), *Zondek & Ticho* (1945), and *Dobyns* (1946), experimenting on animals with extracts from the anterior pituitary lobe, were able to distinguish between a specific thyrotropic and an exophthalmos-producing effect. *Dobyns* further found that the specific metabolic principle, which raises the basal metabolic rate, did not produce exophthalmos.

There is enophthalmos in patients with dystrophia myotonica, besides symptoms indicating reduced functioning of the pituitary gland or its superior centres· gonadal atrophy, cortiadrenal atrophy, reduced meta-

His libido was considerable, and he had become the father of seven children, despite miserable social conditions, and against the wish of his wife

After the disease had been recognized he was recommended for vasectomy.

In 6 of the adult patients (Nos. 19, 24, 44, 70, 120 and 181) the B.M R was determined to be 107, 70, 95, 82, 73, and 82 per cent, respectively *The first patient had no atrophy of testes at the time of examination*, but the others had definite testicular atrophy.

No. 120 was somewhat too heavy, but Nos 24, 44, and 70 were thin in spite of testicular atrophy and reduced B M.R

According to *Hart Hansen* (1941) castration does not affect the B.M R, and the fatness in 15 per cent of castrated persons appears independently of changes in the B M R In many cases the B M R in my patients is reduced and at the same time testes are atrophic, so that the condition is different from that arising from castration

The excretion of sex hormones in the urine was determined in 4 of these 6 patients There was no atrophy of testes in No 19, and the sexual libido was retained. The others had atrophic testes and reduced libido The results of the examinations are

Table 7

Patient No	19	24	70	120	Normal Values
Gonadotropin	45	< 30	< 30	37	< 30 R U
Testicular hormone	6	2	1	3	5—25 H U
Estrin	8	< 20	< 20		< 20 M U
Atrophy of Testes	—	+	+	+	
B M R	107	70	82	73	100 per cent

It appears from this investigation that the excretion of testicular hormone in patients with pronounced testicular atrophy is below normal. Apart from this fact, there were no other abnormalities. The excretion of gonadotropin and estrin was essentially equal to that in normal persons

In three cases the testes had been removed at autopsy, which gave me an opportunity of making histological examinations (patients Nos 120, 181, and 53) In No 120 the testes were slightly atrophic, in No 181 moderately atrophic and soft, and in No 53 seriously atrophic, the size of pigeons' eggs only

The histological examinations revealed varying degrees of atrophy In No 120 there was atrophy in the epithelium of the convoluted tubules, but in certain places the spermiogenesis was retained In No 181 there was likewise atrophied epithelium, but the spermiogenesis was nowhere retained, and in No 53 there was practically no

Waring, Ravin & Walker (1940) attempted the same treatment on four patients, three of whom had atrophy of testes, but were unable to notice any definite effect. *Franceschetti* (1942) tried Slauck's glycine and testosterone propionate treatment, but with no effect.

Own Investigations.

There are among this writer's patients 53 males; 3 are children; 2 are aged sixteen, and 2 are nineteen

Of the adult patients above twenty, 3 (Nos. 10, 102 and 104) have not been examined for atrophy of testes and genitalia, and the investigation therefore comprises 43 adult male patients with dystrophia myotonica.

Of these 43, 6 did not have atrophy of testes (Nos. 27, 93, 101, 105, 127, and 159) while the remaining 37 (or 86 per cent) had more or less pronounced testicular atrophy and dystrophy of external genitalia. In three cases the atrophy was only moderate. testes were of almost normal size, but softer of consistence than normal In other cases the atrophy was extremely severe, so that testes were the size of hazel nuts. In these cases considerable dystrophy of the external genitalia was invariably found; further, the sexual potency was very reduced or completely absent.

The relation between testicular atrophy and age of manifestation of the disease will appear from the following observations. The 6 patients without testicular atrophy first noticed the disease at the average age of 29.7. The remaining 37 had noticed the disease at the average age of 18.6

This limited material does not offer sufficient basis for definite statements, but the evident difference in ages of manifestation makes it probable that atrophy of testes is most pronounced in patients with early age of manifestation.

The relation between testicular atrophy and muscular dystrophy may be elucidated in two ways. The six patients without testicular atrophy had the following degrees of muscle dystrophy: 3, 3, 1, 0, 2, 2. As will be noted, the majority of my patients without atrophy of testes had muscle dystrophy to a severe degree. Among the 43 patients I have examined those with severe muscle dystrophy (degree 3) and those with lighter or no muscle dystrophy (degrees 0 and 1) with the view of ascertaining the number of patients with and without testicular atrophy. There were 19 in the former and 15 in the latter group, and in both only 2 without testicular atrophy Thus, there is no clear connexion between muscle dystrophy and atrophy of testes.

One of my patients (No 159) had severe muscle dystrophy and manifest cataract, but no atrophy of testes or dystrophy of external genitalia

GONADS — IN FEMALES

Steinert (1910) was the first who reported menstruation disturbances in women with dystrophia myotonica a woman, aged 34, had prolonged intervals and simultaneous flushes *Lore Haller* (1933) has described a woman, aged 22, who had severe dystrophia myotonica, B M R, 83 per cent, severe cachexia, and long periods of amenorrhea, turning into strong menorrhagia when she was about thirty. The patient had to be castrated by roentgen *Eckerstrom* (1931) *had a patient who suffered from* severe dystrophia myotonica, B M R was 82 per cent. She contracted menorrhagia after having had normal menstruations up to the age of 38 In 1937 he described another patient, who, since menarche, had suffered from evident hypomenorrhea Besides, such menstruation disturbances have been repeatedly reported, and be it noted that the women in question *are most often frigid*

Reports on histological examinations of the internal female genitalia have not yet been published, as, up to now, no autopsy of women have been reported

Own Investigations

Of the 48 women in this material, 5 are children and 5 are over 50. *Further, information on menstruation in 5 sexually mature women is* not available, and the investigation consequently covers only 33 women between 15 and 50

12 of these (Nos 6, 29, 37, 45, 54, 55, 64, 88, 103, 109, 131, and 134) had normal menstruation with normal intervals

6 patients (Nos 26, 28, 32, 61, 81, and 175) had hypomenorrhea, and in three of them the menopause had set in at the ages of 32, 35, ond 41, respectively.

4 patients (Nos 110, 111, 117, and 151) had normal menstruation, *but with irregular and long intervals*

11 patients (Nos 5, 13, 30, 56, 62, 86, 130, 132, 156, 164, and 165) had hypermenorrhea, and 3 of them were treated by endometrectomy. In patient No 62 the histological diagnosis was irregular hyperplasia of the endometrium In patient No 86 the histological diagnosis was chronic endometritis On account of continued bleeding she was subjected to roentgen castration No histological examination of the third patient was made

Thus, there were menstruation disturbances in 21 patients (or 64 per cent) *and hypo-* as well as hypermenorrhea. The two *histological* examinations gave no unequivocal information as to endometrial changes.

epithelium left, and what was left was strongly atrophic. In Nos 120 and 181 there was, in spots, obliteration of the tubuli with hyalin, and in No 53 there were practically only hyaline traces of the tubuli In certain places could be observed a thick, hyaline ring in the tunica propria, encircling a narrowed lumen with a low epithelium remnant

In all three cases there was a considerable degree of fibrosis in the stroma. In No 120 there was no clear hyperplasia of the interstitial cells, but in No 181, and especially in No 53, where the fibrosis was most pronounced, there were, in the fibrous stroma, smaller or greater accumulations of such cells, which in No 53 might constitute large island-shaped formations

Although there is no determination of the testicular hormone excretion available as regards Nos. 181 and 53, the facts of the cases make it exceedingly likely to be greatly reduced. This reduced excretion, thus, rather corresponds to the atrophy of the germinative epithelium and in no way to the number of interstitial connective tissue cells.

Substitution therapy was attempted only on patient No. 24, who received testosterone acetate, 5 mg three times a week, for seven months, and during two of these supplemented by gonadotropic chorionic hormone, 500 M. U. once a week. Later he received testosterone propionate, 25 mg. per week, together with gonadotropic chorionic hormone, 1,500 I. U , but still without effect on testicular atrophy and general well-being

Summary

In this writer's material atrophy of testes has been ascertained in 86 per cent of the adult male patients. The age of manifestation of the disease was higher in patients without, than in those with, testicular atrophy (29.7 years as against 18.6 years), and thus it seems that this affection is most common when the disease manifests itself at an early age. There was no relation between muscle dystrophy and atrophy of testes.

B. M. R. was reduced in 5 patients with testicular atrophy, but 3 of them were thin The excretion of testicular hormone in the urine was reduced in 3 patients, who presented atrophic testes, and not reduced *in one patient* without this symptom

Histological examination of three pairs of testes showed varying degrees of epithelial atrophy, ending with hyalinosis of the convoluted tubules There was fibrosis in the stroma and hyperplasia of the interstitial tissue cells, inversely proportional to the epithelial atrophy. The reduction in testicular hormone excretion almost corresponds to the atrophy in the germinative epithelium.

Attempts at substitution therapy have hitherto resulted in no definite effects.

— IN FEMA

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To obtain an idea of whether the menstruation changes are particularly present in patients with early age of manifestation of the disease, I have computed the average ages of manifestation for the groups without and with menstruation changes. They are 16.4 and 17.7 years, respectively: i. e. no definite difference.

Finally, I have investigated the relation between the degree of muscle dystrophy and menstruation disturbance by computing the average degree as regards patients in the two above-mentioned groups. It was 1 and 1.5, respectively, and this fact may be cited to support the supposition that menstruation disturbances are most frequently found in patients with severe degrees of muscle dystrophy.

Among the 12 patients without menstruation disturbances, 4 are married and have 7 children, and among the 21 patients with such disturbances 8 are married and have 17 children. Thus, there is no definite difference on this point.

Information regarding sexual libido is available as regards 9 patients in the former, and 18 in the latter, group. Respectively 3 and 5 had retained the sexual libido. Also in this field there is no difference between patients without and with menstruation disturbances.

There is a comparatively high proportion of unmarried women, which is certainly a consequence of the almost constantly reduced sexual libido and potency.

In four women of the mature group the excretion of sex hormones in the urine has been examined.

The three first patients had hypomenorrhea, and a few months prior to the examination the fourth was castrated by roentgen on account of metrorrhagia.

Table 8

Patient No	23	32	62	86	Normal Values
Gonadotropin	< 30	< 5	< 30	> 30	< 30 R U.
Estrin	< 20	10	8	20—150	20—150 M U
Testicular hormone	< 1		1		5—25 H.U.
B M R	80	96			100 per cent

The excretion of estrin was reduced in the three patients with hypomenorrhea. The excretion of gonadotropin was not increased, which, on the other hand, was the case in the roentgen-castrated patient. The excretion of testicular hormone was determined in two cases and found reduced, as in the male patients.

In patient No. 32 — having extremely severe dystrophia myotonic and hypomenorrhea at irregular, most often somewhat prolonged, inter vals — the excretion of gonadotropin and estrin has been determined[1] through a whole month, commencing shortly before a menstruation. The following menstruation did not set in until the lapse of an interval of 44 days, so that no determinations were made during the last 11 days

The results, together with those obtained by K. Pedersen-Bjergaard (1936), who examined the urine of normal females, are given in the form of graphs (Figs. 15 and 16)

The excretion of gonadotropin and estrin in my patient is strikingly small and completely devoid of deviation, whereas the normal graphs show comparatively considerable variations and higher values. A single control examination two years later gave the same results: Gonadotropin < 5 R U, estrin 11 M U, and testicular hormone 1.5 H.U

The external genitalia and pubes have in no cases, hospitalized and thus facilitating closer examinations, been clearly deficient The mammae have been comparatively normally developed in all sexually mature females, but they were completely slack in the above-described patient No. 32, who had constantly low gonadotropin excretion (Fig. 12).

4 of the patients have been examined gynecologically, and explorations revealed no abnormalities

Summary

Ovarial atrophy has not been demonstrated at the investigations of this writer's material, but there were menstruation disturbances in 64 per cent of the sexually mature females with dystrophia myotonica, partly in the form of hypomenorrhea and partly as hypermenorrhea The ages of manifestation of the disease was equal in patients without and with menstruation disturbances, but muscle dystrophy was most pronounced in the latter group, indicating a certain relation between muscle dystrophy and the supposed endocrine disturbance

The excretion of estrin was noticeably reduced in 3 patients, all having hypomenorrhea, and in one of these patients, who had extremely severe dystrophia myotonica, the excretion of gonadotropin as well as of estrin was very low and without the normal variations

In the majority of females the sexual libido was slight or completely absent, and a strikingly high number was unmarried Those 12 married had about the normal number of children (24 in all).

The results of the investigation would indicate a functional reduction of the ovary (and, in severe cases, possibly also of the pituitary gland).

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[1] in "Lovens kemiske Fabrik" Copenhagen

THYROID GLAND

Struma was observed by *Steinert* (1909) in two patients, and had previously been described by *Bernhardt* (1899) and *Gaupp* (1900). *Fleischer* (1918) found struma in 14 out of 28 patients from the Tubingen eye clinic, but this may be due to the fact that the town is situated in a struma region. In computing previous reports *Rohrer* (1916) found that one sixth of patients with dystrophia myotonica had struma. *Maas* (1937) noticed struma in 6 out of 26 female and in 2 out of 61 male patients *Berkman* (1935) has noticed a single case of struma with hyper-thyreosis.

Thyroid gland atrophy has been described by *Naegeli* (1917), *Fleischer* (1918), *Foix & Lagrange* (1924), *Faure-Beaulieu & Desbuquois* (1928), and *Achard, Bariety & Desbuquois* (1930), but *Curschmann* (1936) opined that thyroid gland atrophy is a very rare symptom

Basal metabolism in patients with dystrophia myotonica was first examined by *Maas & Zondek* (1920) They found the consumption of oxygen to be small at rest, but three times the normal at work.

Later, a great number of B M. R. determinations have been made, and I have tabulated a number of these results. It appears that the B M. R. is generally more or less reduced The average value of the 48 cases of the table (Table 10) is 87 per cent, but in a number of cases it was between 60 and 70 per cent

Despite the reduced B. M R. no authors have described patients with myxedema, and, as will be seen from the table, only four patients registered low voltage at electrocardiography [*Keschner & Davison* (1933), *d'Antona* (1935), and *Londres* (1935)].

Nor, it further appears, has *hypercholesterolemia* — which according to *Hurxthal* (1934) and *Gilligan* (1934) can be demonstrated in patients with hypothyreosis — been previously reported, although the metabolic rate was but 63 per cent [*Waring, Ravin & Walker* (1940)].

Pathologico-anatomic examination of the thyroid gland has been made in 10 cases There was struma colloides, the size of a clenched fist, in one patient [*Bielschowsky, Maas & Ostertag* (1933)], in the other cases the gland was, macroscopically, of normal size and shape

Histological examination was made on five of these glands *Hitzenberger* (1920) found normal conditions *Guillain, Bertrand & Rouquès* (1932) and *Weil & Keschner* (1927) found, respectively, slightly and strongly distended vesicles The B M R in the last-mentioned of these patients had been 76 per cent *Bielschowsky* and co-workers had a patient who suffered from typical colloid struma with a few bigger cysts and reduced basal metabolism *Keschner & Davison* (1933) found in a patient, whose B M R was 94 per cent, distended vesicles with flattened epithelium, but at the same time with increased, hyaline stroma and isolated lymphocytic infiltrations Most frequently there were distended vesicles and flattened epithelium, and, in a few cases, increased, partially hyaline stroma

Attempts at substitution therapy with thyroidin on account of reduced basal metabolism have been unsuccessful Brock & Kay (1921), Weiss & Kennedy (1924), and Keschner & Finesilver (1925) found no beneficient effect of thyroidin on myotonia, nor on the general well-being, and Mongillo & Serog (1944) tried, without success, thyroidin treatment (1 grain daily) during one month

Own Investigations.

Struma, in this writer's material, was ascertained in 6 out of 43 adult females (Nos 5, 6, 18, 32, 117, and 130), but in neither the children nor the males All these cases of struma were medium-sized, non-pulsating, comparatively firm, and none of the patients presented clinical signs of hyperthyreosis In patient No 32 the B M.R was determined at 95 per cent None of the other patients have been subjected to this examination

Atrophy of the thyroid gland has not been noticed

B. M R was determined in 6 males and 4 females

Table 9

Patient No	Sex	Age	Degree of Muscle Dystrophy	State of Nutrition	B M R
19	m	40	2	thin	107 per cent
24	m	39	1	thin	70 - -
44	m	20	1	thin	95 - -
70	m	38	2	thin	82 - -
120	m	51	3	fat	73 - -
181	m	46	3	medium	82 - -
28	f	35	2	thin	80 - -
32	f	18	3	thin	95 - -
86	f	41	3	thin	102 - -
175	f	36	0	thin	82 - -

B M R averaged 88 per cent, and the majority of patients were thin despite their reduced metabolic rate

None of my patients with dystrophia myotonica had myxedema Beyond frontal alopecia and comparatively slight pubes on atrophic genitalia there were no abnormalities in pilosity Nor was there any remarkable dryness of the skin, and the bowels functioned normally in spite of the low B M R Examination of the heart showed no symptoms of myxedematous heart changes Electrocardiograms showed no low voltages or pronounced bradycardia Cholesterol in the blood serum was normal in 5 patients Of these, No 24 had B. M R of 70 per cent, nor-

mal electrocardiogram, and 260 mg. per cent cholesterol in the blood serum; B.M.R. in No. 181 was 82 per cent, and there were electrocardiographic signs of myocardiac degeneration, almost iso-electric T_I and T_{II}, and negative T_{III}, cholesterol in blood serum: 249 mg. per cent.

Of the 10 patients, in whom the B.M.R. was determined, the 5 males had atrophy of testes and the 4 women menstruation disturbances. Most of them were severe cases of dystrophia myotonica. The average degree of muscle dystrophy was 2.0, but there was no definite relation between dystrophy and metabolic disturbances.

Pathologico-anatomic examination of the thyroid gland was made in three cases (patients No 120, 181 and 53) Macroscopically there were no abnormalities Histological examinations gave the following results

No 120 (male, 51, B M R 73 per cent) vesicles very enlargened on the whole, filled with colloid, without rim-vacuolation but with flattened low cubical epithelium which has more or less spongy cytoplasm No increase af stroma

No 181 (male, 48, B M R 82 per cent) prevailing dilatation of the colloid-filled vesicles, which were without rim-vacuolation, besides there were a number of small vesicles and cell accumulations The epithelium was cubical with spongy cytoplasm Increase of stroma with faint hyalinosis and moderate lymphocytic infiltration

No 53 (male, 36, no determination of B M R) only few dilated vesicles with colloid Smaller vesicles prevailing, and there were many solid cell accumulations Epithelium was high, cubical, and many cells blown out by secretion Stroma abounded, and in the more solid connective tissue layers there was evident hyalinosis and sparse lymphocytic infiltration

These three examinations show dilatation of the vesicles in the two former patients, who had reduced metabolic rate Further, there was increase of and growing hyalinosis in the stroma in the same order as fibrosis and atrophy of testes

Finally it must be mentioned that thyroidin treatment was brought into use on patient No 32 Her B.M R. was about 80 per cent, and rose, after the administration of heavy doses of thyroidin, to about 100 per cent, but apart from the fact that during the first days she felt livelier and that the amenorrhea ceased for a period, she experienced no improvement. On the other hand, she gradually grew restless and nervous. She was already thin, and now further lost weight, and it was therefore necessary to discontinue the thyroidin treatment. For a shorter period the same treatment was used on patient No 24, but without beneficient effect

Summary.

Struma has been ascertained in a number of cases (between one fourth and one seventh), and almost exclusively in females. The diagnosis is generally struma colloides. In one case only was found thyrotoxic struma, which was operated on [*Berkman* (1935)].

The B.M R is very often reduced (to about 87 or 88 per cent) and may be extremely low (60 to 70 per cent) Apart from the above-men-

Table 10

Basal Metabolic Rate, Cholesterol and Calcium in the Blood Serum, Blood Pressure, and Electrocardiogram.

Author	B M R per cent	Cholesterol mg per cent	Calcium mg per cent	Blood Pressure	Electrocardiogram: P—Q Interval	Electrocardiogram
Maas & Zondek (1920)	low			low	prolonged	
Brock & Kay (1921)	101		10.6	100/60		
Keschner & Finesilver (1925)	98					
Curschmann (1925)	67			85/	prolonged	
Birley (1925)	111					
— —	91					
Deusch (1926)	100			90/	normal	
Christensen, J (1927)	85			110/75	prolonged	arythmical
Berg, W (1927)	95			120/75	normal	
Weil & Keschner (1927)	76					
Maas & Haase (1927)	100			90/65		
Daglis (1927)	105		10.6	115/75	0.17 sec	
Faure-Beaulieu & Desbuquois (1928)	85		9.9	140/90		
Barré & Metzger (1929)	87		10.8			
Achard, Bariéty & Desbuquois (1930)	89		11.3	135/90		
Krause & Ellenbeck (1930)	84					
Rathery, Mollaret & Waitz (1930)	88		10.0			
Morgulis & Young (1931)	87		11.0			
Eckerstrom (1931)	82		12.0			
Guillain & Rouquès (1932)	100		10.1	115/90	0.17 sec	left preponderance
— — —	115		10.4	110/60	0.20 sec	
— — —	90		10.2	145/90	0.18 sec	
— — —	68		10.4	180/90	0.19 sec	
— — —				130/70	0.14 sec	
Harvier & Decourt (1933)		150	11.5	130/80	0.18 sec	
Keschner & Davison (1933)	94		10.3	90/60	normal	low voltage
Krause & Schmidt (1933)	102					
Haller (1933)			11.5	105/75	normal	T_1 og T_2 large
Mayer & Luhan (1933)	86		10.7			
d'Antona (1935)	85		9.5	80/	0.24 sec	low voltage of R
— —	78		11.8	85/60	0.19 sec	
— —	86		12.1	95/60	0.20 sec	low voltage of R
Londres (1935)	100					P T_I and T_{III} absent
Claude, Coste & Fauvet (1936)	112			normal	0.18—0.20	
Eckerstrom (1937)	96				normal	
myot (1938)	72	200		110/70		
atzenstein-Sutro (1938)	94	140	10.6			
— —	96	120	11.0			
— —		114	10.7			

Author	B M R per cent	Cholesterol mg per cent	Calcium mg per cent	Blood Pressure	Electrocardiogram P—Q Interval	
Kolb, Harvey & Whitehill (1938)	93		10.0		normal	
— — — —	82		10.0		—	
— — — —	97		10.0		—	
— — — —	102		10.0		—	
— — — —			10.0		—	
— — — —	78		10.9		—	
Mondon & Pasquet (1939)		230		150/80	0.25 sec.	R broad
Waring, Ravin & Walker (1940)	63	180	11.0		0.24 sec	
— — — —	69	148	12.2	138/90	0.20 sec	
— — — —	81	167	9.8	104/80	normal	
— — — —	70	143	10.1	106/80	0.20 sec.	
— — — —				106/70	0.20 sec.	
— — — —	90	230	10.0	116/80		Myocardial degen
— — — —	80	154	10.6	108/74	0.26 sec	
— — — —	74	148	9.3	96/68	normal	
Lups (1941)	101	160	9.7	95/78		
Thiébaut & Plurinage (1943)	90	181	11.2	110/70	normal	

tioned case, no increase of B. M. R has been found in patients with dystrophia myotonica

There are no clinical symptoms of myxedema, although the basal metabolism is very low A few patients are somewhat fat, but the majority are thin despite reduced B M R., and substitution therapy is of no beneficient effect

Histological examinations most often reveal dilatation of the vesicles and flattening of the epithelium In a number of patients, subjected to autopsy, with such histological changes the B. M. R. was reduced, but in *Keschner & Davison's* patient it was 94 per cent. It is, further, possible to demonstrate more or less pronounced fibrosis with hyalinosis, and in my three autopsied patients the fibrosis of the thyroid gland corresponded in degree to the fibrosis of the testes, but was without definite relation to the dilatation of the vesicles.

The reduction in the B M. R. is in no distinct relation to the histological finds, and there are no clinical symptoms of myxedema. It is difficult to offer an explanation of the reduced B. M R., but with reference to the direct effect on the basal metabolism in animals and man of the specific pituitary hormone of the anterior lobe [*Collip* (1939), *Billingsley, O'Donovan & Collip* (1939)], and *Rabinowitch, Mountford, O'Donovan & Collip* (1939)], there is some basis for the assumption that the reduced basal metabolism may be caused by dysfunctioning of the hypothalamus-hypophysis system.

PANCREAS

Lups (1941) described a family in which three siblings with dystrophia myotonica presented typical steatorrhea Besides, two of them had low curves at sugar tolerance tests Examination of the duodenal secretion from one of the patients showed normal concentration of the single enzymes, consequently it is not certain that the occurrence of steatorrhea has anything to do with the exocrine secretion of the pancreas

Non-tropical sprue (*Hess Thaysen*), on the other hand, is frequently accompanied by various symptoms pointing towards deficient internal secretion *Hess Thaysen* (1932) found, for example, symptoms of Addison's disease in two patients, and *Langen* (1937) observed Simmond's syndrome in two patients with sprue. Therefore, there is a possibility that the steatorrhea in Lups' patients is due to dystrophic changes in the endocrine glands and not, as supposed, to dysfunctioning of the external secretion of the pancreas

It has not been possible for me to trace other patients with dystrophia myotonica and steatorrhea, and none of my own patients have had this symptom.

Internal Secretion

The internal secretion of the pancreas in dystrophia myotonica has been investigated in a number of patients fasting blood sugar values as well as sugar tolerance curves have been examined

Blood sugar was determined in fasting patients by *Brock & Kay* (1921), *Weiss & Kennedy* (1924), *Keschner & Finesilver* (1925), *Maas & Haase* (1927), *Harvier & Decourt* (1933), *d'Antona* (1935), *Rymer & Ravin* (1941), *Lups* (1941), and *Horányi & Pohl* (1942), and the results varied between 078 and 131 per cent, only 3 out of 17 patients had less than 090 per cent These figures must, therefore, be regarded as normal

Sugar tolerance tests were made by *Scharnke & Full* (1920), *Brock & Kay* (1921), *d'Antona* (1935), and by *Lups* (1941) on 6 patients The two first-mentioned authors confined themselves to ascertaining increased glucose tolerance The two last-mentioned authors reported comparatively low tolerance curves in 3 patients and normal curves in one. In *Lups'* patient the curve was particularly flat.

Rymer & Ravin (1941) determined the sugar tolerance in 7 patients and 6 normal persons and found normal curves in the patients with dystrophia myotonica

Rymer & Ravin thought that the normal curves registered from the patients implied the absence of any deeper changes in the internal secre- tion of the Langerhans' islands in the pancreas, of the anterior lobe o the pituitary gland, or of the cortex of the suprarenal gland.

It must, finally, be mentioned that no published reports exist of patients with diabetes mellitus and dystrophia myotonica

Pathologico-anatomic examination of the pancreas has been carried out in only three cases *Bramwell* (1923) in one patient found a small pancreas, but made no histo- logical examination *Bielschowsky, Maas & Ostertag* (1933) in their patient, who had died from acute pancreas necrosis, found fat necroses of long-standing and recent date, but they made no histological examination *Hitzenberger* (1920) found the pancreas, macroscopically as well as histologically, to be normal

Own Investigations.

Repeated determinations of fasting blood-sugar values have been made in six of this writer's patients:

Patient No 24 .079 to .089 per cent.
— - 28 .076 to .090 per cent
— - 70 096 per cent.
— - 86· .126 per cent.
— - 93 084 to 086 per cent.
— - 165 100 per cent.

Some of these figures are somewhat low, but they must all be con- sidered normal

Tolerance tests have been made on four patients with 1 gm. of glu- cose per kg. bodyweight in 250 ccm of water.

In Nos. 70 and 86 the curves were completely normal. In No. 70 the value rose, during one hour, from .096 per cent to 202 per cent, and fell, during two and a half hours, down to 127 per cent.

Three tests were made in respect of patient No 28, who received thyroidin treatment on account of low B M.R From the table appears the metabolic rates at each of the three tests.

Table 11

B M R per cent	0 per cent	15 min per cent	30 min per cent	1 h per cent	1½ hs per cent	2 hs per cent	2½ hs per cent	3 hs per cent
79	088	127	150	083	112	100	114	.102
80	097	170	134	120	127	137	122	107
93	090	147	122	122	122	120	102	.093

From this it appears, firstly, that it is impossible to estimate a patient's sugar tolerance on the basis of a single examination. The figures differ not inconsiderably in respect of the two first tests, although the metabolic rate is equal The increase in B.M.R. from 80 to 90 per cent produced no clear difference, and these tolerance curves must, on the whole, be characterized as comparatively normal

In patient No. 93 the curves may be a little low, and the fall slow, but, like the rest, they must be considered normal.

Pathologico-anatomic examinations have been made of three patients, subjected to autopsy (Nos 120, 181 and 53) In all three cases the pancreas was macroscopically normal Histological examinations revealed that the tissue in the two last-mentioned patients was destroyed by putrefaction In No. 120 there were no abnormalities beyond slight fibrosis in the Langerhans' islands It was not possible to demonstrate any such fibrosis in the cadaveric preparations

Summary.

Three patients with steatorrhea have been reported in one single family, but at examination of the duodenum content in one patient normal enzyme concentrations were found Further, there are no facts to support a theory of dysfunctioning of the exocrine gland tissue, and the cases of steatorrhea described are more likely to be connected with dysfunctioning of internally secreting glands

Examinations of blood-sugar when fasting and sugar tolerance tests show that any deeper changes in the Langerhans' islands are out of the question, as increased glucose tolerance was ascertained in only few cases

At pathologico-anatomic examinations no macroscopically visible changes were found, and in only one of my patients was it possible to demonstrate slight fibrosis of the Langerhans' islands at histological examination

Fibroses of this nature have been described by *Torben Jersild* (1945), who found them in two female patients with Simmond's syndrome Both these patients registered somewhat flattened curves at glucose tolerance tests, and, as will be explained later, there are certain points of resemblance between the *non-muscular dystrophies in dystrophia myotonica* and the organic changes in Simmond's syndrome.

SUPRARENAL GLANDS

Chronic insufficiency of the suprarenal gland has been described by *Goldzieher* (1939). Especially conspicuous in the clinical picture is the insufficient functioning of the cortex of the suprarenal gland The sym-

ptoms are: fatigue, hypotension, low blood-sugar and sugar-tolerance curves, disturbed electrolytic metabolism, abdominal disturbances with vomiting, diarrhea and pains, anorexia, and emaciation. As will be noted, this complex of symptoms to a considerable degree resembles Simmond's syndrome

Haller (1933) reported, in a female patient, aged 35, who had dystrophia myotonica, pronounced muscle weakness, low blood pressure and reduced basal metabolism, he thought that this complex of symptoms resembled Addison's disease

Amyot (1938) in his patient found pigmentation of those parts of the skin exposed to light, and he opined that insufficiency of the suprarenal gland was a contributory factor towards the syndrome in dystrophia myotonica A similar pigmentation has been reported by *Krisch* (1917).

Examinations of the electrolytic metabolism, and especially determination of the blood serum potassium and blood serum sodium values, are particularly important when ascertaining a possible malfunctioning of the suprarenal glands. Examinations of this kind on patients with dystrophia myotonica have been carried out only in few cases

Potassium ions have an aggravating effect on myotonia [*Russel & Stedman* (1936), *Kennedy & Wolf* (1937), and *Brown & Harvey* (1939)] *Cumings* (1939) found the potassium content in myotonic muscles to be below normal *Cumings & Maas* (1939) at several examinations found normal serum potassium; and *Harvier & Decourt* (1933), *d'Antona* (1935), and *Horányi & Pohl* (1942), carrying out single examinations, were unable to report definite deviations from the normal values.

The presence of sodium ions has not been subjected to such thorough examinations *Katzenstein & Sutro* (1938) found serum sodium· 594 mg. per cent — a figure far above normal, whereas *Horányi & Pohl* (1942) reported 320 mg per cent — a normal value

There are no reports of abdominal cases or hypoglycemic shocks in dystrophia myotonica. Emaciation, on the other hand, but not anorexia, is a frequent symptom

Thus, there is no abundance of clinical information pointing towards insufficient functioning of the suprarenal glands.

Pathologico-anatomic examination of the suprarenal glands has been made on five patients Adie & Greenfield (1923) reported normal medulla and spotty distribution of the lipoid in the cortex *Weil & Keschner* (1927) in small, under weight suprarenal glands demonstrated normal medullae and irregular composition of the tissues in the cortex. *Guillain, Bertrand & Rouques* found an adenoma, the size of a pea, consisting of clear, cortical cells, otherwise there were no abnormalities *Bielschowsky, Maas & Ostertag* (1933) found surprisingly small suprarenal glands with narrow cortex and pronounced indigence of lipoid Only in the glomerular zone, and in a few other cell

complexes, were there deposits of fat *Keschner & Davison* (1933) demonstrated even more severe changes as, besides fibrosis of the cortex and especially of the fascicular zone, there were various degrees of cell degeneration, and in certain places the reticular and fascicular layers were substituted by a peculiar red, non-vascular edematous substance

Thus, from a pathologico-anatomic point of view there is a certain basis for the assumption of dystrophy of the cortex of the suprarenal gland

Up to the present moment there is but a single report on attempts at substitution therapy *Kolb, Harvey & Whitehill* (1938) tried the administration of cortiadrenal extract, but found it ineffective.

Own Investigations

Fatigue and adynamia were prominent symptoms in a number of this writer's patients, but in certain cases it was difficult to distinguish between this fatigue on the one hand and the laxity and lack of initiative, the characteristic mental change, on the other. Two patients (Nos 85 and 175) without this symptom, and with very inconsiderable muscle dystrophy, suffered from excessive muscle fatigue which made them unable to perform even light work A third patient (No. 86), besides comparatively severe muscle dystrophy, complained of excessive muscle fatigue, which for a period confined her to bed, as she could neither stand erect nor walk The weakness by far exceeded what might have been expected from the degree of muscle dystrophy.

Hypotension to a moderate degree was present in several of my patients Blood pressure was examined in 13 cases. The majority of patients were over 40, and their respective systolic pressures were: 160, 130, 120, 110, 110, 110, 110, 105, 105, 100, 100, 100, and 75.

Fasting blood-sugar values and sugar tolerance curves in the patients examined could not be described as abnormal (*vide* section on Pancreas).

One of my patients (No 70) was admitted to hospital on account of pains in the epigastrium The cause was undetectable, and there was neither vomiting nor diarrhea In the other patients the gastro-intestinal function was normal, but many were thin despite low B M.R.

Serum sodium tests were made only in two cases In one patient (No. 86), who received treatment with desoxycorticosterone acetate, the content prior to treatment was 310 mg. per cent, in the other the serum sodium level was normal — 327 mg per cent The exactitude of the procedure at these examinations is doubtful to such a degree that I have abstained from further determinations of serum sodium until more accurate methods are known

Serum potassium was normal in patient No. 70 (21.5 mg. per cent).

In my material there were not many clinical signs of reduced suprarenal gland function, but it is necessary that further examinations of serum sodium values be carried out before it will be possible to take a final attitude towards this problem.

Pathologico-anatomic examinations were made in three cases (Nos 120, 181 and 53) The suprarenal glands in the first case were macroscopically normal, in the two others they were diminished with narrowed cortex regions One suprarenal gland in No 53 had blood infiltrations and was partly dissolved Histologically, there were in all three patients thickening of the capsule and more or less pronounced fibrosis of the stroma in cortex and medulla In No 181 there were in several places in the cortex small demarcated adenomatoid areas, surrounded by thick connective tissue capsules The structure of the cortex was changed In the two former patients the zonae glomerulosae were extremely indistinctly outlined, but on the other hand the zonae reticulares and the more pigmented parts of the zonae fasciculatae were broader than normal In No 53 the structure of the right suprarenal gland was completely extinct, and in the left there was fascicular structure retained in but few places, the remaining part being made up of irregular small nests of dark small cells The lipoid in the two former cases was mainly found in the outermost layers, and in No 53 there were only few cellular groups with lipoid cells

Substitution treatment with desoxycorticosterone acetate — Cortiron — (Scheering) was tried against the excessive fatigue in the three above-mentioned patients with this symptoms Hand grasp was measured in No. 86; at the beginning of treatment it was between 4 and 7 kg, and it went up to between 10 and 15 kg, where it remained for the duration of the control period during treatment.

The patient was discharged from hospital, and continued control was therefore impossible. The patient received 5 mg per day for about one month. During this period the serum sodium level rose from 310 mg. per cent (135 millimols) to 320 mg per cent (139 millimols). Normal figures are 327 mg per cent = 142 millimols.

Subjectively, the three patients thus treated experienced increasing strength, and the improvement was obvious to everyone. The doses generally administered are 10 mg every other day in series of 12 injections, possibly repeated with intervals of some months.

Summary.

Excessive fatigue and adynamia in some patients with dystrophia myotonica has been construed as signs of dysfunction of the cortex of the suprarenal gland, but there is no special clinical basis for this assumption Pathologico-anatomic examinations, on the other hand, in a number of cases reveal dystrophy with fibrosis of the cortex and atrophy of the epithelium cells, and it is therefore strange that there are no other clinical deficiency phenomena. Attempts at substitution therapy with

desoxycorticosterone acetate on three of my patients resulted, subjectively, in definite improvement of fatigue, and in one case the hand grasp grew in strength after treatment had been embarked upon.

PARATHYROID GLANDS

Lundborg (1904) was the first to take interest in the parathyroid glands in myotonia Theorizing, he arrived at the result that myotonia is caused by a chronic, benevolent hypoparathyroidism His report resulted in a number of investigations, and the demonstration of cataract in dystrophia myotonica further stimulated the interest in hypopara-hyroidism [*Faure-Beaulieu & Desbuquois* (1928), *Rathery, Mollaret & Vaitz* (1930), *Faure-Beaulieu* (1930), and *Meesmann* (1938)].

According to their conception, parathyroid insufficiency in connexion ith myopathia was the cause of the special pathological picture of rstrophia myotonica with cataract

Rouquès (1931), however, during his thorough investigations found no decisive symptoms to indicate that the parathyroid glands play any part in this connexion

Many authors have determined serum calcium in a great number of patients (*vide* Table 6), and in practically all cases the results were normal. *Jung* (1930) applied a special technique of analysis and found hypocalcemia of medium magnitude in four patients, and *Meesmann* (1938) found reduction of the serum calcium at certain periods Inaccurate technique may be the more obvious explanation of his varying results

Up to the present, pathologico-anatomic examinations have been made in only two cases *Bielschowsky, Maas & Ostertag* (1933) found incipient sclerosing, and *Keschner & Davison* (1933) observed central fibrosis and big fat vacuoles in the gland

Substitution therapy was mentioned by *Rouquès* (1931) as being futile or downright injurious, and *Kolb, Harvey & Whitehill* (1938) with para-thor-mone tried to raise the serum calcium level from 10 2 to 11 4 mg per cent without being able to detect any effect.

Own Investigations.

Determination of serum calcium was made in respect of a number of patients (Nos 19, 28, 42, 44, 70, 93, 120, and 181), and in all cases the results were normal, being between 9 8 and 11 6 mg. per cent

In a number of cases attempts have been made at producing Chvostek's and Trousseau's signs, but it has been impossible to ascertain any signs of latent tetany.

Pathologico-anatomic examinations were made on patients Nos 120 and 181, in whom the parathyroid glands were successfully isolated The histological picture was normal in both cases In No 181 there were a number of follicles and some fat vacuoles

In No. 19 attempts were made at raising the serum calcium level by treatment with dihydrotachysterol (*A. T. 10*); doses were 5 mg. twice daily for a fortnight. Before treatment there was 11 4 to 11 6 mg. per cent, and after treatment 10 8 mg. per cent; thus, the result aimed at was not attained Neither subjectively nor objectively were there any traceable changes

Summary

There have been ascertained no definite symptoms of dysfunction of the parathyroid glands, and histological examinations have revealed no certain abnormalities.

There is, therefore, no basis for assuming the presence of dystrophy in the parathyroid glands

PITUITARY GLAND

The hypothalamus and the hypophysis, according to *Westman* (1943) *form a functional unit, and it may, consequently,* be impossible to refer dysfunction to one or the other part of this unit.

Up to the present the most important symptoms of dysfunction have been ascribed to lesions of the pars anterior of the pituitary gland, and the clinical picture resultant from such severe lesion in this part is termed Simmond's syndrome *Sheenan* (1939) has given a good description of this syndrome, which develops especially in females after postpartum necrosis of the pituitary gland proper, and he maintained that extensive destruction was necessary for the appearance of the syndrome. There is, however, not always quantitative relation between the pathologico-anatomic finds and the clinical picture, and typical histological changes of the pars anterior may be demonstrated in some patients who did not present symptoms of hypophysial deficiency Pressure by tumors or cysts on the pituitary gland or on the hypothalamic region may in certain cases cause a similar syndrome [*Plummer & Jaeger* (1938)], but the majority of the reported cases of Simmond's syndrome is due to anorexia nervosa In such cases there are either no changes in the pituitary gland, or there are only displacements in the relation between the single types of cells in the pars anterior

The clinical picture of Simmond's syndrome is somewhat varied, and has a number of symptoms in common with dystrophia myotonica.

Emaciation is found in a number of patients with either disease. According to *Sheenan* this symptom is not, as stated by previous authors, a cardinal symptom of Simmond's syndrome, as, out of those cases that have with certainty been diagnosed at autopsy, only one third is under-nourished — some are even well-nourished

Asthenia is a constantly occurring symptom of Simmond's syndrome and has also been described in dystrophia myotonica The same applies to *mental changes* with indolence, lack of initiative, and somnolence. There has not been found anorexia in cases of dystrophia myotonica

Progeria with wrinkled, inelastic, thin skin and possibly grey hair is a common symptom of Simmond's syndrome, but in certain cases there may also be myxedema, which gives the patient a somewhat altered appearance These changes of the skin have not been described in dystrophia myotonica

The *basal metabolism* is generally reduced in Simmond's syndrome, but not always are there corresponding pathologico-anatomic changes in the thyroid gland, nor myxedema In dystrophia myotonica similar reduced basal metabolism has been found without more marked thyroid changes or myxedema

Gonadal dystrophy with hypomenorrhea or amenorrhea and other wasting symptoms attached to the genitalia is constantly appearing in Simmond's syndrome It is frequently found in male patients with dystrophia myotonica, and probably also in females as the clinical symptoms described are of a similar nature

Sugar tolerance is frequently increased in Simmond's syndrome, and hypoglycemia may occur during terminal periods *Kirketerp* (1944) thought that hyperplasia of the insular pituitary gland tissue might occur and cause this change in the sugar metabolism As regards dystrophia myotonica descriptions are available of only light and doubtful changes in the sugar tolerance

The similarity between the two complexes of symptoms has been noted by some of the authors on dystrophia myotonica [*Maas & Haase* (1927), *Lemierre, Garcin & Laplane* (1932), *Keschner & Davison* (1933), *Haller* (1933), *Claude, Coste & Fauvet* (1936), *Amyot* (1938), and *Waring, Ravin & Walker* (1940)] without deeper penetration into the problem Several of them thought it possible that hypofunction of the pituitary gland might be the cause of all the non-muscular changes, and *Netter* (1938) and *Richet, Maranon, Pergola & Gras* (1938) imagined that muscle dystrophy might be of hypophysial or hypothalamic origin.

A few authors have noticed polyuria of a nature as in diabetes insipidus [*Steinert* (1909), *Harvier & Decourt* (1933), and *d'Antona* (1935)]

X-ray examination of the sella turcia have been made in a number

of cases. *Claude, Coste & Fauvet* (1936) and *Amyot* (1938) found the posterior clinoid process to be hypertrophic and the sella diminished; in the rest of the cases the sella was normal.

Up to now pathologico-anatomic examination of the pituitary gland and of the hypothalamic region has been carried out on five patients *Adie & Greenfield* (1923), *Weil & Keschner* (1927), and *Guillain, Bertrand & Rouquès* (1932) demonstrated no clear histological changes in the pituitary gland apart from small cysts in the pars intermedia These were also found by *Bielschowsky, Maas & Ostertag* (1933), who, besides, in the pars anterior found increasing numbers of more or less granulated, acidophil cells with small nuclei and single hypertrophic principal cells *Keschner & Davison* (1933) found reduction in the number of epithelium cells and hyperplasia in the connective tissue of the pars anterior, in the middle of which were found practically none but acidophil, more or less degenerated, cells and uncommonly large basophil cells with homogeneous cytoplasm The examination of the hypothalamic region, made by *Weil & Keschner* in 1927, displayed all degrees up to complete degeneration of the cells in the tuber cinereum and the supraoptic nucleus, the rest of the authors found no clear abnormalities *Foix & Nicolesco* (1924) who examined this part of the brain in a patient with myotonia (without further clinical description) found atrophic lesions with ample lipochrome and vacuolation of the nerve cells

Thus, up to the present there have been no demonstrations of typical, certain pathologico-anatomic changes in the hypothalamus or in the pituitary gland — only in a few cases were there atrophy and fibrosis in the pars anterior of the pituitary gland and degeneration of the nerve cells in the hypothalamic region

In a few instances substitution therapy has been attempted *Kennedy & Wolf* (1937) and *Waring, Ravin & Walker* (1940) made attempts at treatment of four patients, two of whom experienced no effect whatsoever, in the two other cases the effect obtained was not convincing despite treatment during extremely long periods

Own Investigations.

In several of this writer's severely affected patients the clinical picture presented a number of features in common with Simmond's syndrome as described above, one of them had been treated according to that diagnosis before the myotonia was recognized by me.

The majority of patients were thin, and some (Nos 32, 93, and 97) are most correctly described as almost horrifyingly emaciated (Figs. 12 and 14), but none suffered from anorexia

Asthenia, more or less pronounced, was a very frequent symptom, and in three patients (Nos 85, 86, and 175) it was a dominant symptom, treatment of which was attempted with desoxycorticosterone acetate

Mental changes with indolence, lack of initiative and somnolence were, as described in the chapter on Mental Changes, very often found.

Progeria and myxedematous changes have not been noticed by this writer in his patients, only alopecia was observed

The B M. R. was considerably reduced in many patients, but without simultaneous myxedematous changes It averaged 88 per cent and thyroidin treatment was of no beneficient effect



Fig 14
Dystrophia myotonica (patient No 93) Excessive emaciation — especially of face enophthalmos and myopathic facies

As mentioned in the section on the Thyroid Gland, there is a possibility that the reduced metabolic rate is caused by hyposecretion of a specific hormone from the pars anterior of the pituitary gland, directly affecting the basal metabolism [*Collip* (1939), *Billingsley, O'Donovan & Collip* (1939), and *Rabinowitch, Mountford, O Donovan & Collip* (1939)]

Gonadal dystrophy was present in 37 out of 43 males (86 per cent) and probably present in 21 out of 33 females (64 per cent) Simultaneously the sexual potency was reduced in a great majority of the patients.

Sugar tolerance was not definitely changed in the patients examined in this respect, and it was impossible to establish symptoms of hypoglycemia

In a great number of patients I have observed a symptom which has not previously been given attention enophthalmos It appears very frequently on the many photographs of patients with dystrophia myotonica published up to the present The presence of this symptom may be brought in to support the theory of reduced functioning of the hypo-

thalamos-hypophysis system, as extract of the pars anterior may in animals produce exophthalmos independently of the thyrotropic and the specific stimulating effect on the basal metabolism [*Dobyns* (1946)].

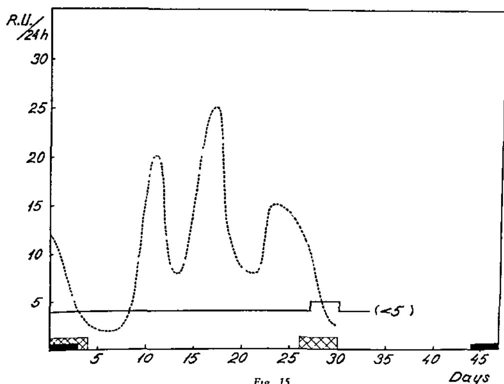


Fig 15

Excretion of *gonadotropin* in urine

———— in patient with dystrophia myotonica (No 32)
— — — in normal female (*Pedersen-Bjergaard*)

The excretion of gonadotropin in the urine was examined in four adult males and four adult females (Nos. 19, 24, 70, 120, 28, 32, 62, and 86).

In seven of these patients the excretion per day was only tested at the routine examinations at which no further titrations were made when the values did not exceed the maximum normal value of 30 R.U.

In patient No. 19 there were 45 R.U. of gonadotropin At that time the patient had no definite atrophy of testes, but he later developed this symptom His excretion of testicular hormone was 6 H.U, which is somewhat below normal

The other seven patients had no increased excretion of gonadotropin, but, as mentioned, the routine examinations do not reveal reduced excretion.

In No. 32 titration of gonadotropin and estrin excretion was made for a period of a whole month The patient suffered from hypomenorrhea and had prolonged intermenstrual periods. It appeared that the excretion of gonadotropin and estrin was constantly very low (less than 5 R. U. and 10 M U, respectively) For the sake of comparison Fig. 15 gives the excretions in the urine of normal females as found by *Pedersen-Bjergaard* (1936). In examinations carried out in the period between two consecutive menstruations he found considerable variations in the excretion of gonadotropin and also of estrin (Fig. 16). My patients with dystrophia myotonica had a constantly reduced excretion of gonadotropin and the possibility cannot be excluded that similar changes might be demonstrated in regard of other patients, provided hormone titrations were carried out during longer periods Single examinations of 24 hours'

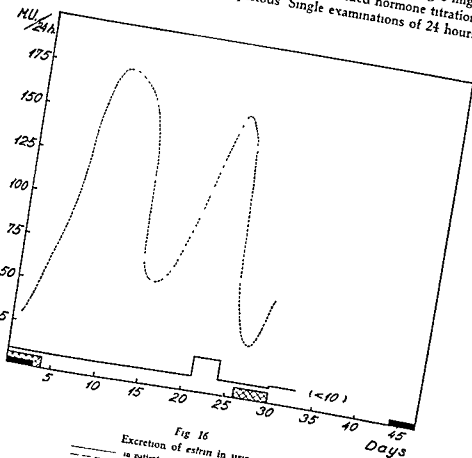


Fig 16
Excretion of *estrin* in urine
——— in patient with dystrophia myotonica (No 32)
– – – in normal female (Pedersen-Bjergaard)

urine are no proper bases for deciding whether the excretion of gonadotropin is reduced

Roentgenography of the sella turcica was made on 7 patients (Nos. 24, 28, 32, 42, 54, 93, and 165); in all cases it was of normal size In patient No. 53 were found, at autopsy, big posterior clinoid processes which narrowed the entrance to the sella turcica.

At the same time the fact must be mentioned that internal frontal hyperostosis was found in patient No. 120 (at autopsy) and in No 165 (at roentgenography).

Pathologico-anatomic examinations were made on Nos 120, 181 and 53 In all three cases the pituitary gland presented, macroscopically, no abnormalities. Histological examinations revealed moderate fibrosis and big blood sinusoids in the pars anterior of Nos 120 and 181, but no definite atrophy of the parenchyma In No. 53 there was neither fibrosis nor atrophy In all three patients the relation between acidophil, basophil, and principal cells was estimated to be normal, but in all three there was, in places, a number of cellular changes with varying size of nuclei, density of chromatin, granulation and formations of vacuoles, but no coarser changes In No 120 there were a number of small follicles in the pars anterior, and some bigger cysts covered with flat epithelium in the pars intermedia Beyond these observations there were no abnormalities in the partes intermedia and posterior

Attempts at substitution therapy were made in respect of No 24 who received 1,000 I. U. of gonadotropic chorionic hormone three times a week for one month; later administrations were 1,500 I U. together with 25 mg. of testosterone acetate three times a week for ten weeks. It was impossible, subjectively as well as objectively, to ascertain any results.

Summary

The clinical picture in dystrophia myotonica has a number of features in common with chronic Simmond's syndrome, and examination of gonadotropin contents in the urine revealed definite reduced excretion in one patient This fact supports the supposition, based on the clinical symptoms, of hypofunctioning in the hypothalamos-hypophysis system

Pathologico-anatomic examinations in some cases showed lighter changes in the pars anterior of the pituitary gland with more or less pronounced fibrosis and, as a rule, comparatively doubtful changes of the epithelial cells Definite atrophy has been noticed only by *Keschner & Davison* (1933).

It is impossible to appraise the exact condition of the epithelial cells in these autopsy preparations which have not been fixated until 12 to 40 hours *post mortem.*

The degenerative cellular changes in the hypothalamic region, which have been described in a few instances, must be regarded with all reserve, as the brains in question have remained unfixated for many hours. A

further investigation of the brains, and especially of the hypothalamic regions, will — in co-operation with *Larus Einarsson* — be made on the present writer's autopsied patients, and the results will be published at a later date.

No definite proof of dystrophic changes in the hypothalamos-hypophysis system has been offered as yet, but reports of a number of symptoms and the results of special investigations may support the view that dystrophia myotonica is accompanied by changes in the functioning of that system A critical pathologico-anatomic examination of the diencephalon, and especially of the hypothalamic region, is certain to yield further elucidation of the problem

ALOPECIA

Alopecia was noticed by *Steinert* (1909) He found partial alopecia in 5 out of 6 male patients and mentioned that from the illustrations of previous reports could be observed the same baldness in several cases

Later, frontoparietal alopecia has been noted as an extremely frequent symptom in males, less frequent in females [*Maas* (1937)]

Generally, the pilosity is otherwise normal Certain authors report reduced growth of beard, thin eyebrows, and reduced truncal and axillary pilosity [*Brock & Kay* (1921) and *Maas & Haase* (1927)]

Faure-Beaulieu & Desbuquois (1928) opined that calvities was due to parathyroidal insufficiency, but, as previously stated, any such theory is without foundation, and nail defects, as in latent tetany, have never been reported [*Rouquès* (1931)]

Frontoparietal alopecia has, further, been ascribed to pluriglandular insufficiencies [*Naegeli* (1917)] and to dysfunction of the hypothalamos-hypophysis system [*Keschner & Davison* (1933)]

Own Investigations

Of this writer's patients with dystrophia myotonica, 46 adult (i e over 20 years) males have been examined for alopecia. More or less pronounced frontoparietal alopecia was found in 38 (83 per cent). Normal pilosity was found in all 7 males under 20.

Those 8 non-alopecic males were aged between 22 and 48 (average age 30) They had comparatively slight muscle dystrophy (average 1.1), but 5 of them had testis atrophy. Thus, there may possibly be less tendency to alopecia among patients with slight muscle dystrophy, but there is no definite relation between alopecia and the trophic condition of the gonads

Of 31 adult (aged over 20) female patients examined for alopecia, only 5 (16 per cent) had thin frontoparietal pilosity. This was also the case in a female patient of 18, but the other 8 aged under 20 had normal hair.

The 5 alopecic females were aged between 26 and 64 (average age 36). They were all emaciated, and 3 of the 4 females between 20 and 50 had menstruation disturbances. The 5 alopecic females had muscle dystrophy to a medium degree (average 1 4). On the basis of these figures it is impossible to say whether there is any relation between alopecia, muscle dystrophy, and possible gonadal dystrophy.

Alopecia in patients with dystrophia myotonica most frequently sets in between the ages of 25 and 30. It is localized frontally and gradually spreads across the crown of the head, but acomia has never been observed. This typical alopecia, together with the myopathic facies, gives the male patients a very characteristic appearance, and from photographs it may often be assumed that the person depicted had dystrophia myotonica (Figs. 8, 9, and 11)

In some patients with severe dystrophy of the genitalia the pubes was but slight, but beyond these observations I have noticed no definite pilose anomalies

Summary

Frontoparietal alopecia is found in approximately 83 per cent of male patients above 20, but comparatively rarely in female patients. The non-alopecic males had relatively slight muscle dystrophy, but there was no definite relation to the trophic condition of the gonads. Alopecia is a fairly typical symptom in male patients, but its cause is unknown.

VASOMOTORIAL DISTURBANCES

Steinert (1909) noticed that two of his male patients had vasomotorial disturbances as they were liable to have cold hands, fits of paresthesia, and cadaveric paleness of the fingers. Such disturbances had already been mentioned [*Schönborn* (1897), *Hoffmann* (1900), *Fürnrohr* (1907), and *Chvostek* (1909)), and they have later been described by many authors. *Waring, Ravin & Walker* (1940) reported that the majority of their patients complained of cold hands and feet and had more or less pronounced acrocyanosis, whereas *Rouquès* (1931) in his patients observed only light symptoms of vasomotorial disturbances, even in cold weather.

The cause of these vasomotorial disturbances is unknown. It has been imagined that they formed part of a more general disturbance in the

superior vegetative centres [*Curschmann* (1936)], but these speculations are of a purely theoretical nature Treatment of the symptom has not been the subject of any discussions.

Own Investigations.

This writer's first patient with dystrophia myotonica (No 19) applied for hospitalization on account of severe vasomotorial disturbances with supersensibility to cold, turning his hands and feet blue, and fits of vasospasms with paresthesia, and senseless, chalk-white fingers. Besides these phenomena, the patient felt, when subjected to cold temperatures, the myotonia more of a hindrance and his muscle strength reduced.

In the family of this patient there was an inherited tendency towards contracting these vasomotorial disturbances, as the mother and several siblings suffered from these symptoms, but is was impossible to demonstrate other symptoms of dystrophia myotonica in the said family members. Such inherited appearance of vasomotorial disturbances has not been noticed in any of my other 20 families with dystrophia myotonica

Vasomotorial disturbances of a similar nature, but generally to a smaller degree, were found in 29 of 49 males and in 27 of 34 females with dystrophia myotonica, totalling 67 per cent There was no definite relation between these disturbances and other non-muscular symptoms, but in patients with vasomotorial disturbances the muscle dystrophy was slightly more pronounced than in patients without those disturbances (1 4 and 1 2, respectively).

No attempts have been made at treating the vasomotorial disturbances Acetylcholine or prostigmine might come into consideration, but the former is of little effect on such conditions and the latter will aggravate the myotonia Applying lumbar sympathicus blockade to patient No 19 I succeeded in producing warmth and reddening in one foot, lasting for some hours Whereupon the cyanotic colour returned

Summary

Vasomotorial disturbances, localized in hands, and, possibly, feet, manifesting themselves by supersensibility to cold, cyanosis, fits of vasospasms with paresthesia, paleness and loss of sensibility are found, more or less severely, in about two thirds of patients with dystrophia myotonica. There is no certain relation between these disturbances and other non-muscular changes, but the degree of muscle dystrophy is a little more severe in patients with than without vasomotorial disturbances. The cause is unknown, and as a rule the symptom is not subjected to treatment.

CARDIAC CHANGES

Subjectively felt cardiac symptoms are exceedingly rare in dystrophia myotonica. *Londres* (1935) had a patient with myocardiac degeneration, but without insufficiency symptoms. He died of syncope anginosa. *Harvier & Decourt* (1933) described a patient with temporary fits of bradycardia and polyuria, and *Mondon & Pasquet* (1939) and *Evans* (1941) three patients with dyspnea and palpitations.

Objectively, symptoms indicating functional changes in the myocardium have been noticed in a number of patients.

Bradycardia is a fairly frequent symptom, but as a rule the heart rate is only slightly reduced (50 to 55). In single instances the rate may be lower and in such patients temporary heart block and atrial flutter have been observed [*Frey* (1925), *Biörk* (1944), and *Evans* (1944)].

Blood pressure in these patients is practically never increased [*Waring, Ravin & Walker* (1940)], and moderate reduction has been noted in a number of cases [*Maas & Zondek* (1920), *Guillain & Rouquès* (1932), *d'Antona* (1935), and *Evans* (1944)]

Roentgenography. Enlarged or diminished heart shadow has been reported by *Harvier & Decourt* (1933), *Londres* (1935), and *Evans* (1944), but in most cases the size of the heart shadow was normal [*Waring, Ravin & Walker* (1940)]

Evans, in his patients, found normal heart tones in only 3 out of 13, but otherwise no authors record any abnormal findings at heart stethoscopy.

Electrocardiogram Deviations from the normal ecg have been reported in a number of cases (Table 10). *Maas & Zondek* (1920) were the first who demonstrated delayed conduction (P-R interval), but since then this symptom has been found in a number of patients, and it must be considered comparatively common. *Curschmann* (1925), *d'Antona* (1935), *Mondon & Pasquet* (1939), *Waring, Ravin & Walker* (1940), *Ask-Upmark* (1943), *Hess Thaysen* (1943), *Biörk* (1944), and *Evans* (1944) in their patients found prolonged P-R interval — above .20 sec — and, as stated, several of *Biörk's* and *Evans'* patients had temporary heart block and atrial flutter

Deformation of the ventricular complex and change of amplitude have been ascertained in a number of patients, and *Evans* in his patients commonly found notching of the Q-R-S complex and low voltage of the P wave. The general reduction of voltage, found in myxedema, has not been described in dystrophia myotonica.

Pathologico-anatomic examinations have been made in comparatively few cases *Bramwell* (1923) found a diminished heart of dark, brownish colour *Adie & Greenfield* (1923) found a macroscopically normal heart *Guillain, Bertrand & Rouquès* (1932)

ascertained slight hypertrophy in the left ventricle, and *Keschner & Davison* (1933) found, macroscopically, ample quantities of epicardiac fat and lipoid infiltration of the myocardium. Histologically they found some muscle fibres in the right ventricle substituted by fat. *Londres* (1935) found in a patient, who had had electrocardiographic signs of severe myocardiac degeneration, macroscopically visible endomyocarditis and aortic sclerosis, and histological examination revealed changes in the myocardium similar to those of the diaphragm. *Segura & Lanari* (1941), examining macroscopically and histologically, found no abnormalities.

These few pathologico-anatomic investigations have revealed no definitely typical changes in the myocardium in dystrophia myotonica.

Own Investigations

Subjectively, none of this writer's patients have had cardiac symptoms. Some of the patients were admitted to neurological or medical wards, and in a number of these cases examination of the heart, with determination of pulse rate and blood pressure, roentgenography, and electrocardiography, were made. Pathologico-anatomic examinations were made in three cases.

In some patients the pulse rate was somewhat slow (54—60), but I have found no cases of severe bradycardia or signs of heart block.

B. P. was generally somewhat low. In most cases tested, the patients were over 30, and the following systolic pressures were ascertained: 160, 130, 130, 120, 115, 115, 110, 110, 105, 100, 100, 90, and 75. The moderate hypotension may be connected with the general weakening resulting from the dystrophic changes in the endocrine glands. Arteriosclerosis has not been ascertained in any of my patients.

Roentgenography of the heart was made in five cases. No. 32 had a slightly broadened aorta and small heart shadow, and No. 181 had slightly aortic ectasia. Size and shape of heart shadow was normal in Nos. 13, 24, and 70.

In none of my patients has ausculation revealed definite alterations of the heart sounds.

Ecg. was made in 12 cases. In No. 181 there was left preponderance. T_I and T_{II} were almost isoelectric, and T_{III} faintly negative. The initial complex in No. 148 was somewhat broad, but in the rest of the patients the ventricular complex was normal. P_I and P_{III} were very low in No. 86, but there have otherwise been demonstrated no definite changes in the amplitudes of the waves. The conduction was delayed in Nos. 66, 70, and 148, being 21 to 22, 24 to 30, and .24 sec. respectively [Ecg. of these three patients have previously been reported by Hess Thaysen (1943)]. In the remaining patients the P-R interval did not exceed .20 sec.; most often it was between 18 and .20 sec.

Pathologico-anatomic examinations revealed macroscopically: No. 120 had a small, brownish heart (weight 320 gm — normal weight 360 gm) Nos 181 and 53 had hearts of normal size without any pathological changes but somewhat diffuse coronary sclerosis in No. 181 Histological myocardiac examinations in Nos 181 and 53 showed normal conditions.

Summary.

Subjectively cardiac symptoms are very rarely felt. Objectively moderate bradycardia and comparatively low blood pressure may frequently be demonstrated. Electrocardiograms may in a number of cases show delayed conduction and in a few instances heart block and atrial flutter. In the majority of patients, however, the P-R interval is less than .20 sec. Finally, degeneration of the ventricular complex may be found in a number of cases.

By pathologico-anatomic examinations it has in a single case been possible to demonstrate changes which correspond to the dystrophic muscular changes, but otherwise histological myocardic examinations revealed no abnormalities

Discussion.

The changes described above, and especially the delayed conduction, has been associated with myotonia [*Ask-Upmark* (1943)], but as they have not hitherto been demonstrated in patients with Thomsen's disease [*Souques & Routier* (1933) and own investigations], it is not likely that this theory can be upheld.

Considering the fact that the changes have hitherto been reported in patients with dystrophia myotonica only, there is more reason to assume that the cardiac symptoms are of a dystrophic nature. *Londres* (1935) thought that the histological picture of the myocardium presented changes similar to those in the striated musculature, but this single finding has not received later confirmation.

In progressive muscle dystrophy there are in certain cases electrocardiographic changes that might indicate severe myocardiac lesions [*Berblinger & Duken* (1929), *Schliephake* (1939), and *Boas & Lowenburg* (1931)], and on pathologico-anatomic examinations changes with lipoid infiltration and fibrosis have been demonstrated. These changes are somewhat similar to those of dystrophic muscles, but it remains to be clarified whether the resemblance is more than superficial [*Globus* (1923) and *Berblinger & Duken* (1929)]. Changes as severe as those here described are not found in dystrophia myotonica, neither electromyographically nor pathologico-anatomically.

It can with some certainty be said that the myocardiac changes in dystrophia myotonica are of a functional nature, as they must be varying in intensity when the heart block occurs temporarily [*Björk* (1944) and

Evans (1944)]. Further explanation cannot be offered, but it is desirable that a thorough histological investigation of the myocardium, and especially of the bundle of His, be instituted.

SKELETAL CHANGES

Some patients with dystrophia myotonica have bone deformations and in others are found changes in the thickness and structure of the bony tissue.

Jaw deformity with narrow superior maxilla, high palate, and abnormal position or deficiency of teeth has been reported in many patients. *Curschmann* (1905) noted that one of his patients had "adenoid habitus". Later *Rohrer* (1916), *Adie & Greenfield* (1923), *Maas & Haase* (1927), *J. Christensen* (1927), *Devry & Everard* (1936), and *Kolb, Harvey & Whitehill* (1938) have, *inter alia*, described such deformation of the jaw *Katzenstein-Sutro* (1938) *especially stressed this jaw anomaly* with its irregular position of teeth and found it in family members with, as well as without, dystrophia myotonica, they did, however, regard the jaw deformation as the result of a dystrophic process in the skeletal system.

In this connexion mention must be made of the fact that habitual jaw dislocation is common in dystrophia myotonica [*Hoffmann* (1906), *Chvostek* (1909) and many others].

Other deformations, especially of back and legs, are comparatively frequently found. *Naegeli* (1917), *Fleischer* (1918), *Ruben* (1919), and *Devry & Everard* (1936) in several of their patients found accentuated thoracic kyphosis or lumbar lordosis and, in a single case, lumbar kyphosis. There is a single report of talipes cavus and genua valga.

There are 15 reports of *roentgenography* of the cranium. In 6 of these cases the sella was small [*Brock & Kay* (1921), *Rouquès* (1931), *Claude, Coste & Fauvet* (1938), and *Amyot* (1938)]. In such cases the posterior clinoid processes were most frequently big and projected strongly forward thus narrowing the entrance to the sella. The sella was normal in the other cases *Lemierre, Garcin & Laplane* (1932) found the cranium somewhat decalcified, whereas *Rouquès* (1931), *Mondon & Pasquet* (1934), *Claude, Coste & Fauvet* (1936), *Amyot* (1938), and *Thiébaut & Plurinage* (1943) in about half of the cases investigated found the theca cranii, and in single instances also the basis, to be the seat of diffuse hyperostosis. In the other half of examined patients the cranial bones were normal.

Roentgenography of other bones has been carried out in a few cases. *Rouquès* (1931) in 4 patients found condensation and thickening of the

cortex of the long bones. No definite deformation or structural changes in the bones of the columna or of the extremities have otherwise been ascertained.

Own Investigations.

Jaw deformation as described above — with high palate, abnormal position, and frequently deficiency, of teeth — was noticed in many of my patients and especially in those with pronounced myopathic facies and dystrophy of mastication and throat muscles. It is impossible for me to say whether the dental deficiencies are connected with the disease in other ways than through the lack of initiative and deplorable financial position of these patients. Several of the patients have, by their respective physicians, been labelled as having adenoid habitus. Tendency to jaw dislocation was found in 2 patients.

Accentuated lumbar lordosis and thoracic kyphosis may fairly frequently be observed in patients with severe degrees of dystrophy of back and abdominal muscles. Recurvated knees, talipes equinus and claw-foot may be noticed in severe degrees of dystrophy of the lower extremities. No other skeletal deformations have been observed.

At roentgenography of the cranium were found normal conditions in 5 out of 7 patients. In Nos. 54 and 165 there was diffuse hyperostosis, and in No. 165 hyperostosis frontalis interna. At roentgenography of the extremital bones there were no abnormalities.

Pathologico-anatomic examinations revealed diffuse hyperostosis in the crania of Nos. 53 and 120. In No. 53 the clinoid processes were big and the entrance to the sella diminished, and in No. 120 was ascertained hyperostosis frontalis interna.

Summary.

In patients with dystrophia myotonica are found jaw deformations, accentuated curvations of the back, recurvation of legs, and talipes equinus and cavus on account of muscle dystrophy; no observations have been made of dystrophy of the bones.

At roentgenography and autopsy there has, in about one half of the cases investigated, been ascertained cranial hyperostosis, some diffuse, others on the internal side of the os frontale.

MENTAL CHANGES IN AND SOCIAL CONDITIONS OF PATIENTS WITH DYSTROPHIA MYOTONICA

In the literature published up to the present, too little attention has, in this writer's opinion, been attached to the mental changes in dystro-

phia myotonica These changes are a very frequent and important symptom, as they greatly determine the extent to which the patients are able to shift for themselves. Not only the muscular, but to an even higher degree the mental, changes are the reason why so many patients with dystrophia myotonica live under socially bad conditions.

Curschmann (1912) was the first to take interest in the mental changes as part of the clinical picture in dystrophia myotonica. In some cases he noticed intelligence inferiority and often a suspicious attitude. But he found no deviations in the social level of the patients Later authors were now aware of the mental changes, and *Bramwell & Addis* (1913) had two patients with low intelligence, deficient memory, and irritable, querulous temperament The language used by one of these patients was "of the type of indecency generally attributed to schoolboys". With regard to the other, the "inability to obtain regular employment appears to have been due to his mental temperament rather than to physical disability". *Rohrer* (1916) in some patients found retained, in others reduced, intelligence, but the most characteristic features were an indifferent, happy-go-lucky nature, lack of will-power, apathy, and very pronounced somnolence These mental changes have received fragmentary treatment in some of the many casuistic reports [*Grund* (1913), *Baake & Voss* (1917), *Heymann* (1917), *Naegeli* (1917), *Ruben* (1919), *Fischer* (1920), *Schemensky* (1923), *Birley* (1925), *Berg* (1927), and *Maas & Haase* (1927)].

Others — as for example *Hauptmann* (1916) — were unable to find mental changes although the intelligence was rarely very high, and, strangely enough, *Adie & Greenfield* (1923) discovered no characteristic mental changes In their opinion the reason for the comparatively low intelligence was to be sought in the fact that the patients came from the lower social strata, but it is remarkable to notice that all their patients were able to support themselves — some even in positions requiring a considerable degree of intelligence However, many of their patients had temperaments as described above and it was often difficult to make them appear for examination

Curschmann (1925 and 1936) had gradually experienced that patients with dystrophia myotonica had varying degrees of mental inferiority, but rarely severe intelligence defects They were mainly sulky, indolent, and egoistic. As a rule the mental changes in the female patients were of a lesser degree than in the males, and he thought that there might occur familial variations. The mental degeneration almost invariably corresponded in degree to the physical dystrophy *Curschmann* (1936) did realize that the majority of patients had to be content with primitive positions and that many of them were badly off, but he was not aware

of the importance of the relation between the mental changes and the social conditions.

Maas & Paterson (1937), who investigated the mental changes in 29 patients with dystrophia myotonica, in all essentials confirmed *Curschmann's* observations. They found intelligence inferiority in 17 out of 29 patients, and there were practically always mental changes in cases of severe muscle atrophy. In cases without, or with but slight, muscle atrophy the mental changes were not always found, and there were several brain workers among their patients. As characteristic features of dystrophia myotonica they found lack of "go" and initiative and a morbid contentedness which glaringly contrasted with the physical incapacity and frequently miserable environment of these patients. Nor did these authors stress the importance of the mental changes with regard to the social deterioration of their patients.

Rittmeister (1939), who investigated the mental changes in a Swiss family with dystrophia myotonica, on all essential points confirmed the above-described changes in his patients, and he found no mental peculiarities in the healthy members of the family. He did not treat of the social deterioration.

Psychoses of a severe nature have not been reported in dystrophia myotonica, and the patients described by *Stertz* (1912) and by *Maas & Paterson* (1937) had psychotic changes to a slight degree only.

Looking back on the foregoing investigations it is surprising to notice that *Waring, Ravin & Walker* (1940), in their descriptions of patients from the U. S. A., found the mental deficiencies small or completely absent. The temperamental changes, they thought, must be viewed rather in connexion with the physical defects than be associated with special heritable, degenerative mental changes. They further held that there might be familial variations in the mental field.

The social conditions in dystrophia myotonica have been given surprisingly little attention. As mentioned, *Bramwell & Addis* (1913) reported their patient being unable to obtain steady employment on account of mental changes, and *Claude, Coste & Fauvet* (1936) thought that the social deterioration of their patient was due to mental changes. It further appears from a number of the case reports that the patients lived in poor circumstances.

Boeters (1935) thought he found patients with Thomsen's disease and patients with dystrophia myotonica mixed in the families with myotonia, but, as has been stated, his investigations are open to criticism, and it seems that many of the cases reported as myotonia have, in fact, been dystrophia myotonica. *Boeters* was the first to attempt an estimate of the social conditions Among his 43 patients over 30 years of age,

there were 14 invalids, and only 10 had retained almost normal working ability.

Apart from this computation — based on a doubtfully diagnosed material — there were no reports of investigations into the social conditions in dystrophia myotonica and especially not into the significance of the mental changes in relation to these conditions. In 1944 I published a brief preliminary report of the results of my investigations [*Thomasen* (1944)].

Own Investigations

The investigation comprises patients as well as healthy members of the 21 families with 874 living persons, of whom 101 were definite cases of dystrophia myotonica

It proved impossible for me to carry through thorough psychiatric investigations of these many persons because the investigations were made during my travelling visits to the members of the families In a few cases of hospitalized patients special intelligence tests were made, but otherwise I have had to rely on my judgment In cases where it has been possible to have trained psychiatrists check my judgment there was satisfactory conformity between their results and mine

In order to get the most accurate impression of their daily life, I have practically never notified the patients of my arrival. During my conversations with the patients, their relatives, and frequently with their local physicians, I have collected material for estimates of intellectual capacity, initiative, and emotionality; I have confined myself to these three mental qualities which in this disease seem to have undergone the most marked changes. On the basis of information regarding working ability and financial circumstances, collected from patients and their surroundings, and by considering their way of living, I have been able to form well-founded judgments of their social condition.

Healthy Family Members

No mental changes were ascertained beyond single cases of lunacy and congenital imbecility.

Investigations into the social standard through several generations revealed it to remain almost constant within each family. Only in rare cases do family members obtain better positions than their parents. It is thus possible with comparative exactitude to characterize the social conditions of the families by the occupation of the former generations.

In this manner the 21 families, in which dystrophia myotonica occurred, might be thus characterized: 13 were families of workmen or smallhold farmers, i e. unskilled workers, generally living in straitened

circumstances, 4 were families of landowners, farmers, or market-gardeners, 3 were families of skilled artisans; and, finally, one was a family of university men and propertied landowners.

Although it is impossible to draw definite conclusions from such limited material, the investigations do show that dystrophia myotonica does not appear exclusively among the members of the community that are socially worst off

Patients with Dystrophia Myotonica.

First it must be noted that there are no cases of psychosis among my 101 living patients, but a number of them are mental defectives. Taken as a whole, it is evident that there are pronounced mental changes in these patients With regard to their mental condition they glaringly contrast with their surroundings and their families

Typical features are. more or less pronounced intellectual deterioration, considerably reduced initiative, and a satisfied care-free temperament.

Intellectual Deterioration

Intellectual deterioration is very commonly found in children with dystrophia myotonica, and it is frequently stated in respect of adult patients that already at school age their intelligence was deficient, wherefore their school knowledge is extremely limited In a number of cases the intellectual deterioration in childhood was severe to a degree that caused the patients to come under care as mental defectives. A number of my patients live in mental asylums, where the dystrophia myotonica had not been recognized in a single case, the patients were only treated as mentally deficient. Two such cases with severe muscle dystrophies had been labelled with the additional diagnosis of peripheral neuritis.

Taken as a whole, the intellectual deterioration in adult patients is more advanced in cases where the disease became manifest in childhood than in cases where the disease did not become manifest until adult age, but I have not ascertained any familial variation

In order to obtain a practical survey, the intellectual deterioration has been stated in degrees for each patient In cases where intelligence tests have been carried out, the results obtained appeared to correspond to my estimate The deterioration is stated in degrees 0 to 3. Degree 3 denotes intellectual deterioration to below about 60 per cent.

As will be noticed, about one third suffer from intellectual deterioration to a considerable degree, and only between one fourth and one fifth can be considered normally intelligent.

Table 12

Intellectual deterioration	0	1	2	3
101 patients	24	41	25	11
88 (aged between 15 and 60)	18	40	22	8
8 (under 15)	3		2	3
5 (over 60)	3	1	1	

Reduced Initiative

In many cases reduced initiative is obvious already in childhood At school these patients are described as lazy and uninterested, and when they leave school their parents, as a rule, find it extremely difficult to get them started in a trade Training in skilled work, for example as artisans, is very rarely completed, and the great majority of such attempts are failures the patients become errand-boys at modest wages, or they may be found in their parents' homes after several vain attempts at some lighter occupation Generally the parents and the employers do not know that these persons are sick, and they always denounce them as lazy, careless in work, and devoid of initiative It is still worse that several cases, by their respective physicians, have been construed in the same way and not as sick persons

In this connexion mention must be made of the fact that these patients, as a rule, are very easily overcome by sleep and difficult to wake up in he morning For a young male patient of mine his master had to have installed a big alarm bell connected with the alarm clock, this was the only way to make him get up in the morning The wife of another patient was in despair because her husband always fell asleep, this might happen in trams or when seated at table — an unfortunate incident when they were entertaining guests

This mental change is also found in patients in whom the disease has not become manifest until adult age Consequently, despite their moderate degree of muscle dystrophy and intellectual deterioration, such patients are, nevertheless, unfit for work No one will employ a lax, lazy, and uninterested worker

An example of the consequences of this reduction of initiative may be briefly cited He was 16 when I first saw him, he had well-developed muscles definitely with myotonia, and his intelligence was medium He was apprenticed to a painter, but the master was distressed about him as apprentice He was very immature frittered away his time was careless and lacked initiative Besides, he was somnolent and his master several times caught him sleeping in a far corner of the work-shop Needless to say his training was bad, and shortly after he had served his apprenticeship — having unsuccessfully made a number of trials as a journeyman painter he had to abandon all ideas of

circumstances; 4 were families of landowners, farmers, or market-gardeners; 3 were families of skilled artisans; and, finally, one was a family of university men and propertied landowners.

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As will be noticed, about one third suffer from intellectual deterioration to a considerable degree, and only between one fourth and one fifth can be considered normally intelligent

complicated with cataract, they are generally satisfied and cheerful. They have never met me with displeasure, and I cannot describe them as being cross or contrary. In no few of them there is a considerable degree of over-self-esteem: they think they manage excellently although at an advanced age they lead a vegetating life at the cost of public funds or at the expense of their families. Not infrequently does this over-estimation of themselves cause conflicts with the healthy family members, who do not realize that they are dealing with sick persons.

The indolence and carelessness, found in so great a proportion of these patients, must certainly be viewed in connexion with their reduced initiative.

Criminality is no special feature of this disease, notwithstanding the deplorable social conditions. Sentences have been passed on only two of my patients — in one case for procuring, in the other for receiving stolen goods.

SOCIAL CONDITIONS

It is evident that the disease causes social deterioration. A comparison of the social conditions of the patients with those of the healthy members of their families shows that the former, if managing on their own, live in circumstances which are either similar to those of their parents or inferior; improvements are never found, and the majority of them are unable to manage without public or family relief.

I have scaled the social conditions of my patients 0 till 3. 0 denotes social conditions as in healthy family members and that the patients are capable of performing normal work. 1 and 2 indicate working ability — and consequently financial conditions — to be impaired to a slight or a more serious degree, and 3 is the degree used for patients so disabled that they are unable to live by their work, but must anticipate their own funds or receive subsidies in one way or another. Such aid generally takes the form of invalidity pension. When reaching the age of 60, the patients, irrespective of their disease, are entitled to old age pension, which is of about the same value as invalidity pension.

As will be seen from Table 14, *54 of the 88 patients in the working age group (between 15 and 60) must be considered invalids in the eyes of the law, their working ability being less than one third. The percentage is 61.5.* Of these 54, 5 are under care as mentally deficient, and the majority of the remainder receive invalidity pension. The 8 patients with severely reduced working ability 2nd degree live in very straitened circumstances.

continuing in that trade With the passing years he had developed dystrophy of various muscle groups and intellectual deterioration, in both respects to slight degrees, but the main cause of his disability is reduced initiative He now receives invalidity pension

Reduced initiative in women is of considerable consequence: they become slovenly, negligent, and careless with themselves and their work. In respect of young, unmarried women the consequence is that after a few short employments they have to go back to their homes. As to married women, *this reduced initiative will leave* deep marks on their homes, and I might relate many a sad story from my visits to these homes

They were invariably very dirty and extremely untidy with cast-off clothes strewn about on chairs, with saucepans containing the remains of old food, and unwashed eating utensils in the kitchen, *with unpolished windows, dirty curtains,* etc. The patients themselves were untidy, with undressed hair, dirty clothes — and completely indifferent In a couple of homes it was strange to observe how they had mended their husbands' clothes with big, multicoloured patches, in no way matching the colour of the clothes, and which had been roughly sewn on to the outside of the material to be mended.

To obtain a practical survey I have classified the reduction of initiative — in degrees varying from 0 to 3 — as has been done in respect of intellectual deterioration.

Table 13

Reduction of Initiative	0	1	2	3
101 patients	20	18	30	33
88 patients (aged 15—60) . .	13	16	28	31

From this table appears that the initiative is reduced to a considerable degree in three fifths of the patients, while only between one fifth and one sixth have retained their initiative.

Reduced initiative frequently goes alongside with intellectual deterioration, but there is a number of cases with severe reduction *of initiative* coupled with slight intellectual deterioration; and some patients, having muscle dystrophy as well as intellectual deterioration to but slight degrees, are, nevertheless, severely disabled on account of reduced initiative (patients *Nos. 37, 42, 63, 94, and 128)*

Temperament.

The temperament in the majority of patients is exactly as described by *Maas & Paterson* (1937). Despite miserable living conditions, suffered by most of the patients, and despite their physical disability, possibly

Among 61 patients with up to 1st degree muscle dystrophy the average intellectual deterioration was 1.08 and initiative reduction was 1.33; in the remaining 40 patients with severe muscle dystrophy the figures were 1.44 and 2 36, respectively Therefore, severe mental changes, and especially severe degrees of reduced initiative, are found in patients with severe degrees of muscle dystrophy

Computations of the average degree of muscle dystrophy in patients with no or 1st degree intellectual deterioration and of patients with 3rd degree intellectual deterioration (imbecility) give exactly the same results: 1.27. In patients with normal intelligence this degree, however, is only .56

From these results appear that though there is a certain relation between muscle dystrophy and mental changes, it cannot be said that the two forms of dystrophy evolve side by side in respect of degree.

Results of Writer's Investigations.

The mental changes take the form of reduced intelligence and initiative and a peculiar emotionality Only between one fourth and one fifth of the patients are normally intelligent, and between one fifth and one sixth have retained their initiative In one third there is considerable intellectual deterioration, and in three fifths there is considerably reduced initiative The changes in temperament may be more or less pronounced, but are almost invariably constant

Besides the mental changes I have investigated the social conditions, which had dismally deteriorated because of the disease. The healthy family members retain their normal social level, and the families are found in all strata of the population Of the patients, seventy per cent are either completely unable to, or can only with the greatest difficulty, shift for themselves, and live in bad financial circumstances. Aid in one form or another is given to 61 5 per cent of the patients Only 6 out of 88 live under social conditions which correspond to those of their healthy family.

Further investigations into the cause of this social deterioration have revealed that muscle dystrophy and intellectual deterioration are greatly contributing factors, but that reduction of initiative also plays an essential part.

Of the 88 patients, only 6 are completely non-disabled by their disease and live in social conditions corresponding to those of their healthy families.

Definite social deterioration has thus been established in 62 out of 88 cases: 70 per cent.

Table 14

Patients between 15 and 60.

Working ability		Muscle Dystrophy				Intelligence Deterioration				Reduction of Initiative			
		0	1	2	3	0	1	2	3	0	1	2	3
Normal	6	5	1			6				6			
Slightly reduced	20	9	11			8	11	1		7	9	4	
Severely reduced	8	1	4	3		1	4	3			2	4	2
Under $^1/_3$ (inval pens)	54	1	18	17	18	3	25	18	8		5	20	29
	88	16	34	20	18	18	40	22	8	13	16	28	31

An investigation into the causes of this social deterioration may take the form of Table 14, which shows the degrees of muscle dystrophy, intellectual deterioration, and reduction of initiative in respect of each of the above-mentioned social categories. It appears that all patients with 3rd degree muscle dystrophy and intellectual deterioration are completely disabled. The figure covering 2nd and 3rd degree muscle dystrophies and intellectual deterioration does not at all comprise all the severely disabled patients; it must be supplemented by a certain number of patients with severe degrees of reduced initiative.

The conclusion must therefore be that social deterioration in dystrophia myotonica is not solely due to physical disability with muscle dystrophy but in an equally high degree to mental causes with deterioration of intelligence and, especially, of initiative.

Muscle Dystrophy in Relation to Mental Changes

As previously mentioned it has been reported several times that severe mental changes are found in patients with severe degrees of muscle dystrophy. Bearing this fact in mind I have compared the degree of deterioration of intelligence and initiative in patients without or with 1st degree muscle dystrophy with that of patients with severe (2nd and 3rd degrees) muscle dystrophy.

Among 61 patients with up to 1st degree muscle dystrophy the ave age intellectual deterioration was 1 08 and initiative reduction was 1.3 in the remaining 40 patients with severe muscle dystrophy the figure were 1.44 and 2 36, respectively Therefore, severe mental changes, and especially severe degrees of reduced initiative, are found in patients with severe degrees of muscle dystrophy.

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C. GENETICS

GEOGRAPHICAL DISTRIBUTION OF DYSTROPHIA MYOTONICA

The first reports on dystrophia myotonica came from German and British authors. *Hoffmann* (1906), *Steinert* (1909), *Curschmann* (1912), *Batten & Gibb* (1909), and *Greenfield* (1911). Later years have seen an appreciable number of casuistic reports from these countries as well as a few greater works: *Fleischer* (1918), *Boeters* (1935), *Adie & Greenfield* (1923), and *Maas & Paterson* (1939—1943).

Some of the best descriptions, as regards heredobiology as well as ophthalmology, originate from Switzerland: *Frey* (1925), and *Vogt* (1924). One of the few greater works is French: *Rouquès* (1931), and there are further casuistic reports from Italy: *d'Antona* (1935); U.S.S.R.: *Pjatnitsky* (1935); Hungary: *Horányi & Pohl* (1942); Sweden: *Herner* (1941); and from most other European countries.

During later years *Ravin* & co-workers in the U.S.A. have investigated dystrophia myotonica. Single reports are known from Japan: *Yokomori* (1920). No descriptions of dystrophia myotonica in other coloured peoples have come to my knowledge.

In Denmark the disease has been known during only a brief span of years The first description was published by *Ladekarl & Stürup* (1938), but after I began my investigations and published a short series of cases in 1940, the disease has been noticed in a number of patients, some of whom were described in 1942 by *Eigil Hess Thaysen*. In my opinion dystrophia myotonica is no rare disease in this country; this has been confirmed by the fact that I accidentally came across three new propositi in the street.

Judging from the facts as they appear in Denmark I think that I am justified in concluding that dystrophia myotonica is commonly distributed, but comparatively rarely recognized in white — and possibly also in coloured — peoples.

DISTRIBUTION ACCORDING TO SEX

Rohrer (1916) in his survey of reported cases of dystrophia myotonica found that the disease appeared far more frequently in males. *Fleischer* (1918) investigated a family with the disease and found the females to be in the majority. Addition of the materials provided by *Fleischer, Frey*, and *Henke & Seeger* in their thorough family investigations gavs as results: 51 males and 50 females. *Maas* (1937) in his comprehensive material found 112 males and 92 females; and in a great

number of patients (547) *Maas & Paterson* (1943) found the disease equally distributed among males and females.

Henke & Seeger (1927) found no clear difference in degree of manifestation between males and females, but *Maas* (1937) and *Maas & Paterson* (1943) found the severe degrees mainly in males, and *Boeters* (1935) found the incomplete clinical picture to be a preponderantly feminine feature.

The present writer's material comprises 53 male and 48 female patients in various age groups. Further, there are 2 males and 2 females with probable, but not verified, dystrophia myotonica. Among the dead there are several more or less certain cases of the disease — 17 males and 21 females. Finally, there were 10 males and 6 females with cataract, but without definite muscle symptoms. Total: 82 males and 77 females. In order to assess the distribution between the two sexes, the number of propositi — 14 males and 7 females — must be deducted. Result: 68 males and 70 females. Therefore, also in my material does the disease appear to be equally distributed among males and females.

In respect of the 101 living patients investigated I have estimated in figures the degrees of muscle dystrophy, intellectual deterioration, reduction of initiative, and the social conditions. These various symptoms and aspects I have compared in order to ascertain their distribution as between males and females. Further, I have in each case compared the age of the patient with the age of manifestation of the disease; these two factors must not differ essentially when it is proposed to utilize the material for comparing the degree of the disease as distributed among the two sexes.

Average age of the 53 males was 32.5 years, and of the 48 females 32.6 years. The respective ages of manifestation were 19.8 and 19.0 years. The male and female groups may therefore be described as satisfactorily uniform with regard to age.

Table 15

	Males	Females
Age of patients	32.5	32.6
Age of manifestation	19.8	19.0
Degree of muscle dystrophy	1.6	1.0
Degree of intellectual deterioration	1.3	1.2
Degree of reduction of initiative	1.8	1.7
Socially (patients between 15 and 60)		
Working ability below 33 per cent	71 p.c.	49 p.c.
Working ability considerably reduced	6 p.c.	13 p.c.
Working ability slightly reduced	23 p.c.	25 p.c.
Working ability retained	0	15 p.c.

The degree of muscle dystrophy — with regard to muscles of consequence on physical working ability — is greater in males than in females, and a considerably higher proportion of males are severely disabled; no males, but 15 per cent of the females, have retained their working ability. There are no definite differences in the mental changes in the two sexes.

The explanation of the striking difference between males and females in group "Working ability below 33 per cent" must in all probability be sought in the fact that manual work makes greater call on the muscles in males than in females. Marriage to many women is a shielding harbour when working ability is reduced

To sum up. My investigations have demonstrated that the disease is found equally distributed among identical age groups in males and females; that the muscle dystrophies are, generally, more severe in males than in females; that there are no definite differences in the mental changes, but the males are, socially, worse off than the females.

Is the disease more frequently inherited through one sex or the other? — Like *Maas & Paterson* (1943) I have counted the number of patients with male and with female inheritance There were 55 patients, who had inherited the disease through 30 male parents, whereas 41 patients had inherited it through 24 female parents. Thus, in my material — as in that of *Maas & Paterson* — the disease is inherited equally frequently through males and females

AGE AND EXPECTATION OF LIFE OF PATIENTS

Fleischer (1917) in his family investigations found that the age of patients with dystrophia myotonica rarely exceeded 50 years. This statement cannot, however, be taken quite literally. *Ravin & Waring* (1939) listed some of the patients reported up to that time and found several aged over 50 The average age of parents in their list is 56 years. Also *Maas & Paterson* (1943) have a number of patients between 60 and 70. *Julia Bell* (1947) has investigated the problem concerning the age of death and found that not only the patients with dystrophia myotonica but also their healthy siblings has an earlier age of death than that found for the population in England and Wales.

The average age of my living patients is 33.4 years. When the patients are tabulated in age groups of 5 years there appears a steep decline at the age of 50 Five patients are over 60; the oldest is 72 (Fig. 16).

There are 24 dead family members who in all probability suffered

from dystrophia myotonica. Of these, 12 died before the age of 40; average age was 43.5 years.

Fleischer, therefore, is right in stating that patients with dystrophia myotonica as a rule die at a young age and therefore must be regarded as comparatively bad lives.

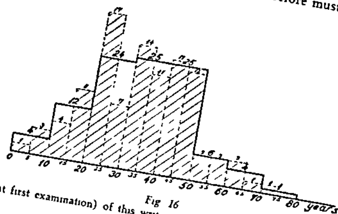


Fig 16

Age (at first examination) of this writer's patients with dystrophia myotonica

AGE OF MANIFESTATION

In casuistic reports as well as in text books it is frequently stated that the age of manifestation of the disease is between 30 and 40: *Rückel* (1937), *Quiros* (1936), *Kinnier Wilson* (1940), *et al Frey* (1925) found the age to be between 20 and 40, and *Maas* (1937) after the ages of 20 to 30, although in his material there were a number of manifestations in childhood. *Curschmann* (1936) stated that the disease rarely manifested itself before the age of 20, and that severe cases never set in in early childhood or in old age *Ravin & Waring* (1939) were of the opinion that dystrophia myotonica — as opposed to Thomsen's disease — most often manifested itself at adult age, but the average age of manifestation in the 57 cases cited by them from other reports was 17.7 years.

In their work from 1943 *Maas & Paterson* still opine that Thomsen's disease and dystrophia myotonica are identical diseases, and they attempt to get round the fact that Thomsen's disease is often congenital, and they underline the fact that they have observed cases of dystrophia myotonica right down to the age of 3 They make no further comments on the age of manifestation

All in all, there have been made no available further determinations of the age of manifestation Such determination is no easy task in respect

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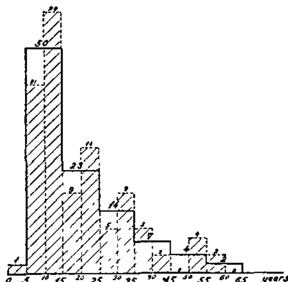


Fig 17
Age of Manifestation of dystrophia myotonica in this writer s patients

FERTILITY IN FAMILIES WITH DYSTROPHIA MYOTONICA

Frey (1925) in his families found no deviations from normal *Henke & Seeger* (1927) worked with a similar material and found the number of children of fertile marriages to be rather a little higher than in the healthy population of the same region *Maas & Paterson* (1943) found the fertility in couples of parents, one of each having dystrophia myotonica, to be considerably reduced, because a certain number of affected persons became impotent at an early age — and especially when they suffered from pronounced myotonia and dystrophy. In those families where the affected parent had but slight symptoms, the marriages were often very fertile *Julia Bell* (1947) found no definite difference in fertility when comparing affected and healthy siblings

I have investigated my own material with regard to differences of fertility in family members with and without manifest dystrophia myotonica or cataract The investigated family members were all children of parents, one of whom had dystrophia myotonica or cataractous changes

In order to make certain that the persons were in the fertile age I have fixed the lowest age limit at 25 years. This limit also ensures, to

of these frequently mentally changed patients. By closely questioning the patients and their relatives and by scrutinizing the family portraits and pictures it has been possible for me to establish an age of manifestation which is not, at any rate, fixed too low, because it is difficult for laymen to notice symptoms of slighter degree. At the first examinations of three children I found no manifest symptoms, but at investigations between one and three years later there were clear symptoms. The children were then 7, 11, and 12 years. In my material there were 8 children under 15 with dystrophia myotonica; the youngest child was 2 years when I ascertained incipient dystrophia myotonica.

A number of patients were unable to give exact statements as to the earliest time of manifestation, but said that it was at the beginning of school age — about the age of 6.

In the living older patients the disease did not become manifest until an advanced age.

Tabulation of the age of manifestation of 5 years' groups results in a curve reaching its maximum at 10 to 15 years with a hyperbolic fall with growing age. Tabulation in 10 years' groups, beginning at the age of 5, gives a far more regular curve. Figures show that the disease manifested itself before the age of 15 in 51 per cent of the patients, before 25 in 74 per cent, and before 35 in 88 per cent Average age of males was 19.8 years and of females 19.0 years (Fig 17)*.

Occasioned by *Curschmann's* statement that severe cases do not set in at an early age, I have investigated the degree of dystrophia myotonica in such patients. It appears that many a severe case did set in in childhood, whereas in none of those 6 cases with manifestation after the age of 50 was the muscle dystrophy so severe as to hamper working ability, and the 2 intellectually deficient cases might equally well have been incipient senile dementia. Such light cases of dystrophia myotonica with late manifestation might well account for the frequently-reported families with parents lacking symptoms of dystrophia myotonica.

My investigations reveal that previous statements, to the effect that the period of manifestation is between the ages of 30 and 40, are untrue. The disease most often manifests itself before the age of 15, but may become manifest at a more advanced age. At this late onset the degree of the disease is invariably very slight.

* *Addendum during proof-reading* On the basis of *Maas'* material and on a material collected from the literature *Julia Bell* (1947) has calculated the age of manifestation adding that such jugdment is a difficult matter The graph depicting these calculations is similar to that of fig. 17 of the present work, reaching its peak at the age of 15 to 20 years The graph based on *Maas'* material however is more flattened out than those on the material from the literature and on the material of this writer

HEREDITY IN DYSTROPHIA MYOTONICA

Already among the first reports on dystrophia myotonica there were several with familial occurrence of the disease: *Hoffmann* (1900) and *Steinert* (1909) *Curschmann* (1912), besides familial occurrence, found signs of degenerative progression with anticipation in the following generation. In the majority of cases the disease seemed to be sporadic, and when i 1916 *Rohrer* computed all available reports, familial occurrence was demonstrated in only 23 out 82 cases, he therefore concluded that familial occurrence was frequent, but not regular

Fleischer (1917 and 1918) was the first who established the regular familial occurrence of the disease. In a family from the Schwartzwald region, Germany, he was able to trace it five generations back through several branches to mutual ancestors Most members of the earlier generations had died, but on the basis of available information he concluded that the disease is inherited latently through 3 to 4 generations, then to appear homologously in the 5th generation of the single families. In the 4th generation there was senile, and in the 5th presenile, cataract with or without muscle symptoms By comparing the patients of the 6th with those of the 5th generation *Fleischer* found progression of the disease· in the 6th generation the onset was earlier and the character more serious than in the 5th. At any rate this progression was obvious with regard to cataract.

Frey (1925) investigated a material from Vogt's ophthalmological ward in Zurich and confirmed the results obtained by *Fleischer*. He also found dominant heredity and progression

Henke & Seeger (1927 and 1928) further investigated Fleischer's family and collected a number of reported cases. They statistically prepared their results and found that the heredity was genetically conditioned, simply dominant and not sex-linked According to their estimate of patients in 5th and 6th generations there was anticipation as well as potensation They imagined that the progression was caused by so-called phenotypic induction the genetically altered soma retroacted on the gene, whereby the disease aggravated with advancing generations

Katzenstein-Sutro (1938) during several years investigated a Swiss family. It was remarkable that the muscular symptoms in this family were inherited only through the males He thought the heredity to be irregularly dominant with varying degrees of expression as a consequence of pleiotropia of the affected gene, he also reported progression in this family.

Weitz (1936) opined that the predisposition originated from mutation and that progressing mutation might lead to earlier onset and more serious course of the disease

a satisfactory degree, that those persons counted as healthy have no latent dystrophia myotonica.

Healthy and affected persons are found in the same sibships, and there are no essential differences in age between the two groups of parents.

Table 17.

Parents' generation	Married	Unmarried	Children	Per marriage	Effective fertility
Healthy	75	11	188	2.5	2.2
Dystrophia myotonica	43	35	115	2.7	1.5
Cataract	11	2	34	3.1	2.6

Thus, there is no reduced fertility in marriages in which one parent has dystrophia myotonica or cataract. But, as might be expected, there is a proportionally high number of unmarried persons among the family members with dystrophia myotonica — a consequence of the changes in the endocrine secretion and of the mental changes, which *inter alia* render the patients sexually uninterested and barren

The present investigation has, therefore, not confirmed that of *Maas & Paterson*, as the fertility in marriages in which one parent has dystrophia myotonica is equal to that of marriages between two healthy parents. The effective fertility, on the other hand, is considerably reduced in patients with dystrophia myotonica.

MORTALITY IN INFANCY AND CHILDHOOD

Frey (1925) and *Henke & Seeger* (1927) investigated — and found increased — infant mortality and frequency of still-births in families with dystrophia myotonica. *Frey*, as later *Maas & Paterson* (1943), thought that the disease caused increased mortality in early childhood. *Henke & Seeger* ascribed the mortality to poverty.

I have in my cases investigated infant mortality in families where one of the parents had dystrophia myotonica. There were 58 infants whose fathers had dystrophia myotonica; 3 died in early childhood. Of 69 infants whose mothers had dystrophia myotonica 12 died in early childhood — a considerably higher proportion. From my own knowledge of the mental changes and the social conditions I am inclined to blame the external environments rather than the disease for this high infant mortality.

Lenz (1936) adopted a policy of waiting, as progression in his opinion was completely incompatible with the ordinary laws of inheritance.

Maas & Paterson (1943) took up the problem of heredity, covering both Thomsen's disease, paramyotonia, and dystrophia myotonica. Their family investigations comprised 97 sibships: 365 persons Of these, 236 were "affected", 103 "suspicious", and only 17 "unaffected". Even if the number of propositi be subtracted, the relation between diseased and healthy by far exceeds 1:1, when those "suspicious" are grouped as diseased. On the contrary, if they are reckoned as healthy the relation is 1.16·1. The symptoms characterizing the suspicious cases are, however, rather vague (weak hand grasp, absence of reflexes, or "some degree of mechanical myotonia"), only the cases having "apathetic myotonic facies" make a more credible impression

In order to explain why the relation between diseased and healthy members of the sibships exceeds 1 1, *Maas & Paterson* had to suppose that myotonic diseases are inherited with multiple factors, which singly may be found in normal persons The absence of single factors, in their opinion, explained the incompleteness of some pathological pictures, for example of cases with absent cataract or muscle dystrophy. To get these multiple factors united one had, in reality, to assume consanguinity, but as it was not strikingly frequent in the present generations they supposed it had been present before the families in question had gone up to London.

Own Investigations.

Material.

The material comprises 21 families in which have been ascertained cases of dystrophia myotonica I have investigated the paternal and maternal families of the propositi, going back until I found other members with symptoms of predisposition; this family was then further investigated, and the results stated in the pedigree. The other family was less thoroughly investigated, but I have in all cases made certain that there were no signs of predisposition in the nearer family of the respective parent of the propositus. I consider this limitation justified in view of the comparatively rare occurrence of the disease

The results of the family investigations are given in pedigrees, one for each of the 21 families, and the investigations cover 1,148 family members, 874 living and 274 dead

Among those living, 101 had certain, and 4 not quite certain, dystrophia myotonica, while 17 had cataract without other symptoms Among the dead, 44 had presented signs of dystrophia myotonica, and 14 had manifest cataract

Herner (1940) investigated a big Swedish family with dystrophia myotonica and found dominant heredity regardless of sex. He makes no mention of progression in this family.

In 1939 *Ravin & Waring* in the U. S A. investigated the heredity in four families and characterized the heredity as irregularly dominant, as some parents might be without symptoms. Comparatively late manifestation in the parents might be the reason why the disease had not been ascertained In their opinion the disease originated from mutation with alteration of the activity of the gene, increasing with each generation. By the hypothesis of a modifying factor, which, in connexion with the mutated gene, might produce cataract, they were in a position to explain the absence of cataract in certain cases. Progression, to *Ravin & Walker*, was not a problem, but an applicable explanation of the irregular dominance.

Maas (1937) found the disease transmitted by dominant inheritance and noted progressive deterioration in 17 out of his 57 families with dystrophia myotonica, but — in his own words — "it does not seem to be an invariable rule." He further thought that there might be indications of fraternal anticipation with earlier onset in the younger members of sibships.

Boeters' work "Über Myotonie" of 1935 treats of heredity in 20 families with myotonia In these families *Boeters* found cases of dystrophic and non-dystrophic myotonia mixed, and he thought this phenomenon an expression of phenotypic differences. *Lenz* (1936) supposed that there must be a special biotype in *Boeters'* material, but when scrutinizing the selected case histories in Boeters' work one cannot but doubt the quality of his clinical investigations. A few examples may be cited· Patient No. 1, in family I was bald, had hollowed temples, protruding lips, and was mentally debilitated. Diagnosis· "Myotonie, Schwachsinn." With those symptoms one would suspect that the patient suffered from dystrophia myotonica. The same holds for patient No. 9 of the same family The patient had myopathic facies and was mentally debilitated, but *Boeters* writes: "Keine Atrophien" and diagnosed "Myotonie." Further, no examinations as to cataract were made, and the abovementioned examples are two out of many. Finally, in over 70 per cent of the patients working ability was severely reduced — a fact pointing towards dystrophia myotonica. In my opinion Boeters' clinical investigations and diagnoses must be disregarded.

Apart from this essential point and working on the hypothesis that the majority of cases were in reality of dystrophia myotonica, it appears from Boeters' investigation that dystrophia myotonica is of dominant, and not sex-linked, inheritance. But he rejected the idea of progression, without stating reasons

is very minimal. This would indicate that there is no inter-familial connexion between the single families. A thorough investigation in this respect has revealed no such connexion.



Analysis of the Pedigrees

Apart from pedigree 11 with its scanty material, the analysis reveals familial occurrence of the disease

The disease may either manifest itself as dystrophia myotonica or in a more monosymptomatic form as cataract, whether manifest or recognizable at slit lamp examination

Heredity in all cases is direct, not atavistic.

Apart from family No. 18, the father of which it has been impossible to subject to slit lamp examination, I have in all cases, where it was possible to examine both parents of patients with dystrophia myotonica, found

Collection of Material

The collection of propositi was made from 1938 to 1943, and the family investigations mainly carried through in the period 1941—1943.

I have been notified of propositi through hospital wards, neurologists, and the Invalidity Insurance Court, but some I have traced myself.

In most cases it has been necessary to obtain information about the families by personal visits, but some knowledge has been gathered by correspondence, by investigations of parish registers and other records.

The family investigations were rendered somewhat difficult during war time travelling conditions, and were complicated by the ever increasing number of propositi.

I have never had any difficulty in establishing friendly contact with the patients — an obstacle reported by a number of previous authors.

Investigation of Material

In the majority of cases the propositi had been admitted to hospitals where, most obligingly, a number of special examinations were made for my benefit.

This writer's investigations of family members were carried out either in their homes or works places. In a number of cases eye examinations were submitted to an ophthalmologist

From family portraits I have in many cases been able to make a probable diagnosis, as the appearance of the patients is likely to be fairly characteristic with myopathic facies and more or less pronounced frontal baldness. In respect of all cases of living patients my probable diagnoses have been confirmed

The mental changes form an outstanding symptom in dystrophia myotonica, and I have attached great importance to investigations in this field

I have investigated for active myotonia in finger flexors, in mastication muscles, and in lower extremities Mechanical myotonia has been searched for in tongue edge, forearm extensors, and in the thenares

Muscle dystrophy has been investigated in facial muscles, mastication muscles, sternocleidomastoid muscles, and in the muscles of the extremities

Further, attempts have been made at ascertaining struma, atrophy and functional disturbancies in the sexual glands, alopecia, and acrocyanosis, and notes have been made if the state of nutrition differed essentially from normal

Slit lamp examinations for cataract were made as extensively as possible — especially in all doubtful cases, but in many instances I have had to confine myself to examining for macroscopically visible cataract.

In a few cases I have followed the patients during a number of years and noticed how slight symptoms became more manifest In three children I have watched the manifestation of the disease.

Geographical Distribution of the Families in Denmark.

On a map of Denmark I have marked the homes of the families. As will be seen, the distribution is even, and the tendency of accumulation

in successive generations led to stronger mutation and consequent earlier onset and aggravated condition. In 1939 *Ravin & Waring* offered a somewhat similar explanation of anteposition and potensation as noticed by them. *Maas & Paterson* (1943) pronounced their views comparatively guardedly. In the family they found degeneration as well as regeneration, but — even allowing for all possible statistical errors — the progressive degeneration was the more prominent feature.

Own Observations on Progression

In regard of my own material I have — in a similar manner as did *Ravin & Waring* (1939) in respect of their own material and that of a number of previous authors — worked out the age of onset and degree of the disease in parents and children In respect of degree I have not confined myself to distinguishing between severe or slight cases, but I have stated the degrees of muscle dystrophy, intellectual deterioration, and reduction of initiative, in the manner explained above. There are in all 34 children, and the results of the investigations are

34 children with dystrophia myotonica, father or mother having the same disease

	Children	Parents
Aage in years	22.7	57
Age of manifestation	11.2	38
Degree of muscle dystrophy	94	1.00
Degree of intellectual deterioration	1.65	.55
Degree of reduction of initiative	1.78	1.30

11 children with dystrophia myotonica or cataract, father or mother having cataract

	Children	Parents
Age in years	30	62
Age of manifestation	20	59

From the above it will be seen that there is, at any rate apparently, anticipation and potensation, especially of the mental defects

Against this, attention must be called to the fact that when dealing with parents we have a selected material of patients with dystrophia myotonica, because it only comprises those who did not become affected so early and so severely that it prevented them from having children. The majority are unmarried and live in straitened circumstances

It is unfortunate that this material does not comprehend a sufficient number of parents with dystrophia myotonica or cataract in successive generations to allow of a regular statistical computation.

Among my families there are two (Nos 9 and 13) in which the generations of parents are practically complete However, in No. 13 a boy died at the age of 9, without definite signs of dystrophia myotonica,

Siblings of Living Parents of Propositi

A considerable proportion of these sibships have died. The parents of family No. 18 have not been included, as the investigation is incomplete There are 43 members of these sibships, of whom only 18 are living 4 had dystrophia myotonica and 5 cataract, 9 diseased in all. Risk: 50 per cent ± 3 7 per cent.

Cousin sibship of propositi and their parents, and children of the affected members.

There are in all 80 such family members, 53 living. Of these 24 have dystrophia myotonica and 3 cataract, 27 affected. Risk. 51 per cent ± 6 9 per cent

When adding the number of members of these sibships having dystrophia myotonica or cataract, the result is 104 affected out of 186 living members After deduction of 18 propositi the risk is 46 per cent ± 3 6 per cent As no correction for age has been employed this result must be regarded as a little too small Reckoning on monohybrid dominant heredity one might expect a risk of 50 per cent in the family groups investigated, provided failing manifestation does not occur. The risk of contracting the disease thus ascertained is so near 50 per cent that it must be reckoned as probable that heredity is as stated.

Progression

As already mentioned this question has been the subject of discussion, most authors who have gone deeper into the problems of dystrophia myotonica maintain that the disease in inherited progressively with anticipation as well as potensation through successive generations *Henke & Seeger* (1927) use the designation of Heilbronner's Law, as in 1903 *Heilbronner* reported anticipation in a family with chronic Huntington's chorea, but, as established by *Maas & Paterson* (1943), this theory on degeneration is still older, as in 1857 *Morel* described degeneration and subsequent death of families with insanity Geneticists like *Lenz* (1927) and *Curtius* (1935) were equally disinclined to believe in progressive heredity in dystrophia myotonica as in other so-called degenerative diseases In *Lenz'* opinion is was not improbable that the severe cases of the disease had been overlooked in previous generations, because it had only been known for a short period, and that it possibly appeared in an aggravated form when its specific gene coincided with other genes *Weitz* (1936) held that considerations of this nature were generally caused by faulty statistics, but that this was not the case in dystrophia myotonica. Here was, in his opinion, a mutation reserve which

Fraternal Degeneration.

The question of progressive degeneration in sibships with dystrophia myotonica was especially investigated by *Maas* (1937) and *Maas & Paterson* (1943). They thought it possible to demonstrate anticipation as well as potensation in younger siblings According to *Fleischer* (1918), dystrophia myotonica appeared in a homologous and homochronous manner in each sibship, i e the pathological pictures present no greater deviations and age of manifestation is almost constant in each single member of the sibships *Ravin & Waring* (1939) did not find the fraternal degeneration so evident as the anticipation from one generation to another, but he considered the phenomenon to be definitely present in many families

Maas & Paterson provided another explanation of the phenomenon, either was the germ plasm affected, or the external conditions — malnutrition for example — acted upon the younger family members in a manner that they contracted the disease at an earlier age and to a more pronounced degree

Investigations of own Material

In 20 sibships examined, having more than one patient with dystrophia myotonica, I have computed the average age, age of manifestation, and degree of the disease in respect of the youngest and the eldest member.

	Age	Age of manifest	Muscle dystrophy	Intellect deteriorat	Reduct of initiative
Eldest	36.6	18.9	1.4	1.35	1.5
Youngest	26.9	17.4	1.05	1.15	1.45

Already this investigation tends to show that there is no definite anticipation and definitely no potensation, as the degree of the disease, as might be expected, is rather more pronounced in those siblings who have had it for the longest period

It is impossible to see whether *Maas & Paterson* investigated the relation between males and females in respect of the eldest and youngest siblings, but it is a relation that must be taken into account, because the disease manifests itself somewhat differently in the two sexes.

Among the 20 eldest there were 12 males and 8 females, while among the youngest there were 9 males and 11 females So the figures are not quite commensurable

Of the 20 sibships I have picked 9 in which the eldest and youngest members were of the same sex, and a comparison between these 9 pairs of siblings gave the following result

and in No 9 there is a married man, aged 56, but without children. All the others are married and have children.

In family No 9 there are 7 investigated children with dystrophia myotonica of 3 parents with the same disease (I have not personally examined patient No 112) In family No. 13 there are 8 children with dystrophia myotonica of 2 parents with the same disease.

The results of investigations in these two families are as follows:

	Family No 9		*Family No. 13*	
	Children	Parents	Children	Parents
Age in years	21	49	29	63
Age of manifestation	10	24	15	55
Degree of muscle dystrophy	1 1	1 4	.5	0
Degree of intellectual deterioration	1.9	1 0	1.5	0
Degree of reduction of initiative	1 7	1 9	1 6	0

From this small investigation appears that of these two families it is safe to say that there is anticipation, and presumably also potensation of the pathological picture in the youngest generation.

From analysis of the pedigrees it becomes evident that one parent in no few cases presents cataractous changes, whereas in the children dystrophia myotonica is fully developed The reverse is never found. My family investigations show that in the older generations there were cases of senile cataract, in the following presenile cataract, and in the third fully developed dystrophia myotonica as well as cases of presenile cataract. The fourth generation has fewer members, because patients with dystrophia myotonica seldom have children. The comparatively few cases having dystrophia myotonica are children of patients with cataract or slighter degress of dystrophia myotonica. Family No. 1 offers an excellent example of the development here described. This development first reported by *Fleischer* (1918), may be considered almost classic, but the possibility of selection in previous generations may be a source of mistake in that only parents with cataract have children, while patients with fully developed dystrophia myotonica generally remain without issue. It is impossible with certainty to exclude such errors until a number of thoroughly investigated successive generations is available.

The investigations of my own material point towards progression of the disease through the generations, the final generation consisting of diseased members without power of propagation — but investigations so far possible have *offered no definite proof of progression.*

The progression as found may be explained by selection in the parents' generations on account of reduced fertility in patients with dystrophia myotonica, but the possibility of real progression cannot be completely rejected.

CHAPTER VIII

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

ARE THOMSEN'S DISEASE, PARAMYOTONIA, AND DYSTROPHIA MYOTONICA IDENTICAL DISEASES?

For some years after *Steinert's* description of dystrophia myotonica the general opinion was — as held by him — that dystrophia myotonica was but a special manifestation of Thomsen's disease, but *Curschmann* (1912) and *Grund* (1913) maintained that dystrophia myotonica nosologically must be classified as a unit, and this distinction has been applied in most later works *Nissen* (1923) found no dystrophic symptoms in Thomsen's family, but his investigations cannot be recognized as being completely satisfactory *Fleischer* (1918), *Henke & Seeger* (1927), and *Vogt* (1924) found no cases of Thomsen's disease in their families with dystrophia myotonica In the greater part of the many casuistic reports on Thomsen's disease and on dystrophia myotonica the dual conception has been maintained, also in the thorough works by *Ravin* and co-workers in the U S. A , published during recent years.

Boeters (1935) in his heredobiologic investigations found cases of Thomsen's disease and dystrophia myotonica indiscriminately in the families with myotonia, but, as already stated, his clinical estimate cannot be depended upon and in this context his comprehensive material must be disregarded

Maas & Paterson (1939) in a literary survey tried to establish as a fact that myotonia congenita (Thomsen's disease), dystrophia myotonica, and paramyotonia are identical affections and that Thomsen's disease, in all probability, is but an early stage of dystrophia myotonica. The only manner in which Thomsen's disease as such could be said to exist was as a familial variant of dystrophia myotonica with tendency to widely spread myotonia and faint manifestation or late development of dystrophy. This, they opined, also held for paramyotonia, and they further expressed as their opinion that if the families were completely investigated it would be possible to reveal dystrophia myotonica in some of the members.

	Age	Age of manifest	Muscle dystrophy	Intellect deteriorat	Reduct of initiative
Eldest	36 0	17 3	1.7	1 55	2 0
Youngest	26 3	16.2	1 7	1 55	2 0

The material of this investigation is too limited to afford sufficient basis for a decisive statement, but it does indicate that there is still no clear fraternal anticipation or potensation with the increase of the number of siblings

Thus, the results of the present investigation may rather be construed to support *Fleischer's* assertion of homologous and homochronous appearance of the disease within each sibship.

Result of Heredity Investigations.

Dystrophia myotonica is a heritable disease. It seems to be inherited dominantly and with varying manifestation, as it may appear monosymptomatically in the form of cataract.

At a first glance the appearance of the disease in the families might indicate progression in the younger generations with anticipation as well as potensation of the pathological picture, beginning with senile-presenile cataract, finally transforming the family members into infertile, dystrophic patients. These observations may, however, be founded on selection in the foregoing generations, caused by the fact that only the least affected patients are able to produce children. Progression can be regarded only as a hypothesis as long as there is no available statistical investigation of several consecutive, completely investigated generations of a number of affected families

Fraternal degeneration with earlier manifestation and potensation of the pathological picture in the youngest members of sibships has been impossible of demonstration in my families

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	Age	Age of manifest	Muscle dystrophy	Intellect deteriorat	Reduct of initiative
Eldest	36.0	17.3	1.7	1.55	2.0
Youngest	26.3	16.2	1.7	1.55	2.0

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Fraternal degeneration with earlier manifestation and potensation of the pathological picture in the youngest members of sibships has been impossible of demonstration in my families.

Thomsen's disease and paramyotonia on the one hand and dystrophia myotonica on the other. In my opinion paramyotonia may be classified as a special variant of Thomsen's disease.

This chapter will be devoted to considerations as to diagnosis and differential diagnosis of these diseases with myotonia, and at the same time give reasons for my opinion that they are not identical

Myotonia.

Myotonia is the common symptom of the diseases described. It is characterized by involuntary protraction of muscle contraction, whether the contraction be voluntary or produced through mechanical or electrical stimulation, there is, however, no protraction of single contractions. At electromyography there is characteristic spontaneous *rest-activity* and electrical activity corresponding to the protracted *contraction*

Generally, myotonia is the first manifest symptom. In Thomsen's disease it most often manifests itself in early childhood, and in many cases it is manifest in infants, which fact has caused the designation myotonia congenita. The same holds for paramyotonia In dystrophia myotonica, myotonia never becomes manifest in infancy, but I have ascertained myotonic symptoms in a child of 2, which to my knowledge is the earliest manifestation of myotonia noticed in dystrophia myotonica Otherwise myotonia at the earliest manifests itself about the age of 6, and most frequently between the ages of 10 and 20.

Localization of myotonia, likewise, varies with each disease In Thomsen's disease, myotonia is most often spread to practically all striated muscles, but it may be found to be more localized, especially in the lower extremities In paramyotonia the myotonic phenomena are *similarly localized* In dystrophia myotonica, myotonia may in rare cases be almost universal as in Thomsen's disease, but in far the greater part of cases myotonia is found only in the muscles of the forearm and in the mastication muscles, and the myotonia never reaches such degrees as in Thomsen's disease. Characteristic of Thomsen's disease is hampered walking, and of dystrophia myotonica difficulty in opening the hand after a firm grasp.

Electromyographically there are no differences in quality between the myotonia of Thomsen's disease and that of dystrophia myotonica.

Alterations in muscle functioning in myotonia can practically never be confused with other diseased conditions, provided investigations are carried out in an adequate manner, especially with regard to electromyography.

Some authors have considered tetany and myotonia identical affections and after Lundborg's report (1904) — on the *effect of the parathyroid gland on certain so-called*

Maas & Paterson cited *Higier* (1916), *Rosett* (1922), *Guillain, Bertrand & Rouquès* (1932), and *Kramer & Quadfasel* (1933) in support of their theory, as those authors likewise considered Thomsen's disease and dystrophia myotonica identical. But they failed to quote *Böe* (1932) who of two brothers with myotonic disease reported muscle dystrophy in the one, but was unable to find symptoms in the other.

When considering critically the above-mentioned reports one notices that their support in favour of *Maas & Paterson's* views is slight

Thus, *Higier* writes that myotonia atrophica is a disease sui generis, but related in nature with Thomsen's disease *Rosett*, in a family covering three generations, found

led *Guillain, Bertrand & Rouques* to advance the theory of steady transition from Thomsen's disease through dystrophia myotonica to progressive muscle dystrophy, these affections were to be regarded as various forms of myopathia Finally, *Kramer & Quadfasel* on the basis of an extremely feeble material pronounced that it was difficult to distinguish the two diseases from one another

In reality, *Boe's* report provides the most weighty immediate support of *Maas & Paterson's* theory, but it is unfortunate that *Böe* investigated only the two brothers when the family had several patients with myotonia, and the diagnosis dystrophia myotonica is not completely definite in the patient who, besides myotonia, had muscle dystrophy in face, neck and upper extremities There was no atrophy of testes, no mental changes, and pilosity was vigorous. Cataractous changes were not looked for by slit lamp examination All in all, the diagnosis must be considered uncertain

Maas & Paterson's foundations for their theory of identity were, as mentioned, of a purely documentary nature They had not themselves had cases that could be labelled Thomsen's disease, but only cases of dystrophia myotonica. With regard to the mental changes in Thomsen's family they opined that a detailed psychiatric examination, if made, would reveal neurotic and mental symptoms corresponding to their description of those symptoms in dystrophia myotonica. As to the early age of manifestation of Thomsen's disease they confined themselves to stating that dystrophia myotonica may sometimes be ascertained in early childhood. Regarding differences in general condition when the patients advance in years, they only mentioned that in certain cases of Thomsen's disease there is general, progressive, physical deterioration As an example was cited Dr Thomsen's grandfather who had had to abandon his military career on account of his disease. Taken as a whole, the arguments in favour of the asserted identity are fairly weak, and in my opinion the authors are in the wrong The present thesis, therefore, deals with each disease separately. In any case, there is a difference in nature between

Trophic Condition of Muscles.

Thomsen (1876) and *Nissen* (1923) described the increased volume of muscles in the patients of Thomsen's family. They presented no muscle dystrophy, and this also holds for the many patients from the literature I have collected in the chapter on Thomsen's Disease.

Batten & Gibb (1909) and *Steinert* (1909) were the first to report the typical localization of muscle dystrophies in dystrophia myotonica, and these dystrophies have been described in many later reports.

Maas & Paterson (1939), however, thought that muscle dystrophy belonged to myotonia, as they considered Thomsen's disease, paramyotonia, and dystrophia myotonica identical diseases In none of their many patients was muscle dystrophy absent. Nevertheless they thought it possible to find patients without clear dystrophy, but were the families of these patients investigated one would be able to find some with dystrophy of muscles. In their opinion the three diseases in question were, in fact, to be characterized as dystrophia myotonica

In my material of 29 patients with Thomsen's disease and 101 with dystrophia myotonica there is a difference in kind between the trophic condition of the muscles in the two groups of affections

In the 29 patients with Thomsen's disease the muscles were, as a rule, diffusely hypervoluminous A few had medium muscle development, but none had muscle dystrophy. As mentioned, in a couple of patients with hypervoluminous muscles the volume of the sternocleidomastoid muscles was normal, they were followed through several years, but it was impossible to ascertain any development of dystrophia. One of the patients was photographed 21 years ago and when comparing with his present appearance one finds practically the same hypervoluminous musculature.

In practically all the 101 patients with dystrophia myotonica was found the characteristic dystrophy of facial muscles, muscles of the throat and neck and possibly also of forearm muscles, but a number of the patients had more widely spread muscle dystrophy Muscle dystrophy provides the patients with a characteristic facial expression, and they more resemble each other than their own relatives Their myopathic facies is unlike the facies found in progressive muscle dystrophy, although there are certain features in common Dystrophy of throat muscles renders speech nasal and indistinct, and the majority of patients speak quickly and monotonously Dystrophy of mastication muscles causes the jaw to drop and the mouth to gape. Dystrophy of neck muscles especially affect sternocleidomastoid muscles and those of the nape The patient therefore finds it difficult to carry his head, and in the majority the head is carried in a bent forward position Dystrophy in the muscles of the forearms

motor neuroses as tetany, myoclonia, myotonia, paralysis agitans, myasthenia, and myatonia — a number of serum calcium investigations on myotonic patients have been carried out Cataract in dystrophia myotonica stirred up interest in the parathyroid gland and revived the old Lundborg theory However, neither clinically nor humorally is there any basis for assuming relationship between tetany and myotonia Tetany is due to functional disturbance in the C N.S, and myotonia is caused by functional disturbances in the muscle fibres Humoral conditions in myotonia show no decrease in serum calcium, and nerve sensibility is normal

Myotonia might be confused with certain peripheral, localized muscle cramps, accompanied by fasciculations (myokymia) and often by pains These cramps especially occur in the calf muscles and frequently in one side only They are generally caused by lesions of the peripheral nerves and are especially met with e g in cases of sciatica, the cramps are often accompanied by muscle atrophy, changed reflexes, deficient sensitivity, and possibly by local perspiratory changes The cramps are produced by a vigorous, voluntary contraction but may also appear resultant from mechanical stimulation of the muscle, or from electrical stimulation of muscle and nerve — especially of the latter [*Higier* (1916)] According to *Denny-Brown & Pennybacker* (1938) this cramp condition is caused by irregular contractions of fasciculi, and the electromyographical registration takes the form of partly amalgamated tetanus with irregular oscillations and intervals The cramp condition seems to be of peripheral origin as it remains even when the innervation is paralysed by spinal anestesia [*Grund* (1919)] In contradistinction to myotonia it is, as stated, accompanied by pains, and the cramp relaxes in jerks Further, it is accompanied by irregular, coarse fasciculations, is often localized, and is accompanied by other phenomena from the peripheral nerves Finally, this condition is not hereditary and is unaccompanied by other symptoms belonging to the "myotonic diseases".

In *Hoffmann's syndrome* in myxedema the functioning of the muscles may be hampered in such a manner as to cause the use of the term myotonia As previously described in Chapter VI there is, in this syndrome, hampering of contraction as well [illegible]

electromyography [illegible] acteristic features of myotonia, and it may therefore at the most be described as a myotonoid functional disturbance This tardiness of muscles is distinguished from true myotonia by closer observation of myxedema, absence of mechanical myotonic reaction, and the brief delay in relaxation following voluntary contraction Once it is realized that the patient has myxedema, the differential diagnosis will not be difficult — and the results of treatment will confirm its correctness

Spasticity and *rigidity* following lesions of the supranuclear motor neuron or lesions of the extrapyramidal motor brain regions are impossible of confusion with myotonic functional disturbances Further, electromyography will reveal the nature of the affection

By way of conclusion it must be mentioned that *idiomuscular reaction* has no connexion with myotonia, and it must not, as is frequently the case, be confused with mechanical myotonic reaction Idiomuscular reaction is a local, slowly subsiding state of contracture without accompanying electrical activity Mechanical myotonic reaction is a fascicular, successively decreasing contraction, accompanied by electrical activity.

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involves considerable reduction of strength of fingers and consequently considerably reduced working ability In more severe cases a number of muscle groups beyond those mentioned may be affected, with the result that carriage is bad with increased lordosis, and walking is hampered by weakness of the quadriceps femoris or of the anterior muscle group of the crus (dropfoot).

Judging from my investigations I would say that there is typical localization of muscle dystrophies in dystrophia myotonica. A couple of patients had extremely slight myotonia without dystrophy, but only one of my patients, a younger woman, at the first examination had no definite muscle dystrophy despite evident myotonia Examination some years later revealed dystrophy of facial muscles. Another patient at the first examination definitely had myotonia, but only slight dystrophy in facial and sternocleidomastoid muscles His other muscles were rather somewhat hypertrophic, especially those of the lower extremities After a couple of years the muscle dystrophies became more pronounced and more widespread, and he now appears like the rest of the members of his family with dystrophia myotonica

Muscle strength in Thomsen's disease is generally medium and rarely corresponds to volume of muscles. In dystrophia myotonica strength is reduced corresponding to dystrophies.

Finally, the musculature in paramyotonia, in trophic respect, seems to be as in Thomsen's disease.

Increased volume of muscles is a frequent symptom in Thomsen's disease, but may also be found in other morbid conditions and may develop as a result of muscle exercise. Hypertrophy does not manifest itself electromyographically The histological reports on biopsy are not quite congruous, but they will receive no further mention in the present work

Increased volume of muscles is a prominent symptom in *Debre-Semelaigne's* and *Hoffmann's syndromes* in myxedema In Hoffmann's syndrome there is, moreover, hampered muscle function, rendering the semblance with Thomsen's disease even more striking This differential diagnosis has been dealt with in the chapter on Myotonia Muscle hypertrophy and muscle fatigue yield to thyroidin treatment Completely normal conditions are found at electromyography

Muscle hypertrophy may occur in *peripheral neuritis* This may be observed for example in persistent cramp tendencies with myokymia [*Bittorf* (1910)] and after polyneuritis [*Krabbe* (1921)] This form of muscle hypertrophy is localized in the muscle [illegible] may therefore frequently be unila- [illegible] pains and swelling will facilitate [illegible] and the differential diagnosis in relation to Thomsen's disease

Pseudohypertrophy in progressive muscle dystrophy may at first sight convey the impression of muscle hypertrophy, but the gummy consistency, the reduced strength, and the development of the disease will clarify diagnosis

In a few cases of *dystrophia myotonica* I have noticed localized hypertrophy of for example the muscles of the lower extremities but it is possible to make the correct diagnosis by considering the characteristic muscle dystrophies and the non-muscular organic dystrophies

Of the above-described differential diagnoses in relation to Thomsen's disease, especially Hoffmann's syndrome has caused confusion, and if brief "myotonia" is found in a patient with rapidly developed diffuse muscle hypertrophy, it is necessary to look for myxedema in order to exclude Hoffmann's syndrome

Muscle dystrophies in dystrophia myotonica are not accompanied by fibrillation, and at electromyography one finds, as in progressive muscle dystrophy, normal interference and no single potentials. In histological preparations is noticed the irregular mixing of hypertrophic and atrophic fibres, as in progressive muscle dystrophy [*Wohlfahrt & Wohlfart* (1935)].

Myatrophies that may be taken into consideration as differential diagnoses in relation to dystrophia myotonica can, according to localization of the cause of myatrophy, be divided into spinal and neurogenic atrophies and muscular dystrophies

Spinally conditioned muscle atrophies are due to wasting of one or more motor nerve cells of the anterior horn Clearly noticeable muscle fibrillation is frequently observed simultaneously with muscle atrophy and reduction of strength At electromyography through three electrodes *Buchthal & Clemmesen* (1941) found single potentials and more or less synchronized action potentials from the three electrodes — an electrophysiological manifestation of lesion of the motor nerve cells of the anterior horn.

The spinally conditioned muscle atrophies are most often localized peripherally in the extremities, and they are rarely hereditary [*Aring & Cobb* (1935)]

Progressive spinal muscle atrophy (Aran-Duchenne) rarely sets in before the age of 20 with slowly progressing muscle atrophy in hands More rarely the dystrophies are localized in shoulder and nape muscles and in the anterior muscles of the crus. There are no symptoms in respect of sensitivity and pyramidal tracts, nor changes in the cerebrospinal fluid

Amyotrophic lateral sclerosis sets in at a more advanced age, but the atrophies develop, on the other hand, more rapidly than in the disease just described, which it completely resembles in other respects However there are almost constant symptoms in the pyramidal tracts

Syphilitic amyotrophic lateral sclerosis has earlier onset and is accompanied by changes in the cerebrospinal fluid with positive W r

Progressive anterior myelitis — or the so-called chronic anterior poliomyelitis — is characterized by rapidly appearing pareses of single muscle groups without typical localization [*V Lunn* (1946)] In these cases are most frequently found changes in the cerebrospinal fluid with hyperalbuminosis and slight pleocytosis

Infantile spinal muscle atrophies (Oppenheim's and Werdnig-Hoffmann's diseases) can hardly come into consideration as differential diagnoses Clinically these diseases manifest themselves through slackness and paresis, especially of the extremities, and there are electromyographical and histological signs of spinal atrophy.

The so-called *peroneal muscle atrophy* (Charcot-Marie-Tooth type) is a hereditary, probably spinally conditioned myatrophy in adults It is inherited dominantly, and generally sets in in the muscles of the foot and in the peroneus area from where it may spread to the lower part of the femur. More rarely it spreads to forearms and hands Frequently there are also peripherally localized sensibility disturbances At electromyography *Buchthal & Clemmesen* (1941) demonstrated a very clearly synchronized electrical activity when leading off through three electrodes from the same muscle. *Wohlfahrt & Wohlfart* (1935), however, at histological examination found a picture corresponding to that of progressive muscle dystrophy

Neurogenically conditioned muscle atrophies are caused by wasting of the motor nerve fibres Muscle atrophy and reduction of strength is most often accompanied by muscle fibrillation, and *Buchthal & Clemmesen* (1941), electromyographically, in this form of myatrophy demonstrated single potentials, but no definite synchronization of action potentials

Progressive hypertrophic neuritis (Dejerine-Sottas) is a familial, but rare, disease which sets in between the ages of 10 and 20, with slowly progressing paresis and special localization in the small muscles of the hand Usually there are, simultaneously, neuritic symptoms with pains and deficient sensibility, sometimes the nerves may feel thickened, but spinal changes are absent

Chronic polyradiculitis is, like the foregoing disease, accompanied by pains and by severe changes in the cerebrospinal fluid

Muscular dystrophies as a rule are hereditary. They are not accompanied by fibrillation Electromyographically there are no single potentials, but interfering activity, because the atrophy of muscle fibres irregularly affects all units of the muscle. For this reason there are no isolated retained units from which single potentials may be led-off without disturbing interference from neighbouring units — as is the case in neurogenic and spinal atrophy

Progressive muscle dystrophy almost invariably sets in proximally in trunk and extremities, possibly also in the face There are various clinical forms of this affection, and varying heredity in these diseases has been demonstrated In contradistinction to dystrophia myotonica, there are generally muscular changes only

As has been stated there is dystrophy of facial muscles in a number of cases, but this affection does not, however, give the patients the facial appearance typical of dystrophia myotonica Nor are throat muscles generally affected, and there is, consequently, no hampering of speech Finally, there is not the typical dystrophy in the sternocleidomastoid muscle

These are the myatrophies to be considered as differential diagnoses in respect of dystrophia myotonica, and it will be noted that, as to localization, the greatest doubt may arise when one faces spinal, progressive muscle atrophy and peroneal muscle atrophy (Charcot-Marie-

Tooth). If electromyography be employed it must be realized that there is no possibility of distinguishing between progressive muscle dystrophy and dystrophia myotonica

Cataract.

Lenticular opacities may be demonstrated in most patients with dystrophia myotonica In slighter cases are found cortical, generally point-formed, grey, white, or coloured shining opacities, and in severe cases there is a stellate, polar cortical opacity, often simultaneously with white or coloured shining grains. Not until transformation into mature cataract does the nucleus become turbid with cloud-like condensations

Such lenticular opacities may also be found in otherwise healthy relatives of patients with dystrophia myotonica These family members are genetic carriers and are frequent among parents of patients.

The opacities have been compared with those of latent tetany, in which disease, however, they are more thread-formed and more subcapsularly localized In myxedema and Mongolian idiocy there may be similar grainy cortical opacities, but seldom the more developed stellate formations

No similar opacities have been found in cases of Thomsen's disease *Knaur* (1936) stated that two dead relatives of patients with Thomsen's disease had had cataract, and *Maas & Paterson* (1939) cited this report in favour of their theory of identity between Thomsen's disease and dystrophia myotonica

Among the members of my families with Thomsen's disease there has been found only one case of manifest senile cataract in an otherwise healthy person. Nor had cataract been noticed in dead family members. Out of 8 patients subjected to slit lamp examination 4 had single uncharacteristic grains in the lens, but there was no turbidity of the above-described type This definitely shows the differences in respect of lenticular opacities between Thomsen's disease and dystrophia myotonica.

Dysfunction of Endocrine Glands

Symptoms of dysfunction of several of the endocrine glands is a typical feature of dystrophia myotonica

Atrophy of testes was ascertained in 86 per cent of adult male patients, and menstruation disturbances pointing towards ovarian dysfunctioning in 62 per cent of adult female patients Excretion of testicular hormone and estrin in the urine was most often reduced and sexual potency and libido were generally very slight or completely absent

B M R in many cases was reduced, at times to a considerable degree (average 87—88 per cent), but symptoms of myxedema were never found There was no definite relation between the histological picture of the thyroid gland as compared with the B M R. and it is possible that

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the reduced basal metabolism may be due rather to dysfunction of the hypothalamus-hypophysis system than to hypofunction of the thyroid gland

Corticoadrenal dystrophy was found in most autopsied patients. Clinically, dystrophia myotonica has certain features in common with Addison's disease, amongst others extremely pronounced asthenia on which desoxycorticosterone acetate is of beneficient effect.

No typical histological changes were found in the hypothalamus-hypophysis system, but in many patients there were, nevertheless, a number of clinical symptoms indicating dysfunction of this organic system Besides gonadal dystrophy, reduced basal metabolism, and corticoadrenal atrophy, *a number of cases presented* excessive emaciation despite good appetite, reduced excretion of gonadotropin in the urine, and enophthalmos.

Muscle dystrophy cannot have relation to dysfunction of the endocrine glands as in cases of progressive muscle dystrophy symptoms of this nature are very rarely met with, and endocrine syndromes resembling those of dystrophia myotonica are never found [*Sjövall* (1936)]

In patients with Thomsen's disease and in their family members without myotonia *I have never found, nor have previous authors reported,* dysfunction of the endocrine glands. *Maas & Paterson* (1939) did not at all treat of these symptoms — showing the definite difference between Thomsen's disease and dystrophia myotonica.

Alopecia

Early frontoparietal alopecia is practically always found in male patients with dystrophia myotonica, more rarely in female patients. The symptom has no definite relation to, for example, atrophy of testes, but, nevertheless, it may probably be regarded as the manifestation of dysfunction of the endocrine glands, because it is absent in patients with progressive muscle dystrophy and in Thomsen's disease.

Vasomotor Disturbances.

Acrocyanosis, possibly accompanied by vasospasms with paresthesia and pale senseless fingers, is exceedingly frequent in patients with dystrophia myotonica These vasomotor disturbances are of another nature than found in patients with paralyses, as they may often be demonstrated without any considerable degree of muscle dystrophy being present. *Sjövall* (1936) reported acrocyanosis and edema in a number of patients with progressive muscle dystrophy, but made no mention of vasospasms which are very troublesome for patients with dystrophia myotonica.

These vasomotor disturbances have not been reported or found in patients with Thomsen's disease.

Cardiac Changes.

Cardiac changes are found in a number of patients with dystrophia myotonica. Only very few feel, subjectively, lighter symptoms, but many have bradycardia and hypotension to a slight degree In a number of cases electrocardiography reveal delayed conduction (.20—.30 sec.), and a few authors have reported temporary heart block with bradycardia. *Evans* (1944) found frequently low voltage of P-waves and deformity of the ventricular complex — but such changes were not typical of my patients

Pathologico-anatomic examinations have provided no basis for supposing that the myocardium is affected by the muscular dystrophy Nor is this an established fact in progressive muscular dystrophy, although in the latter disease there may frequently be severe myocardiac changes, electrocardiographically as well as pathologico-anatomically.

Up to the present, no cardiac changes — clinically as well as at electrocardiography, and especially not in respect of prolonged P-R interval — have been ascertained in patients affected by Thomsen's disease Cardiac changes, therefore, belong among the dystrophic symptoms that contrast dystrophia myotonica to Thomsen's disease

Skeletal Changes

Skeletal changes as reported in dystrophia myotonica are first and foremost caused by muscle dystrophy On the other hand, I have found it impossible to demonstrate dystrophic bone deformities, apart from certain morphologic changes of the facial bones

Hyperostosis of cranial bones, especially of the internal side of the ossa frontalia and of the posterior clinoid process, may be connected with dysfunction of endocrine glands, as such hyperostoses may be found in certain endocrine gland affections

No skeletal changes were ascertained in patients with Thomsen's disease.

CHAPTER IX

THERAPY

Treatment *of the symptom myotonia* has already been dealt with in the chapter on that affection *Quinine* in large doses (1—1.75 gm. daily) *is of a brief beneficial effect in the same manner as is insulin in diabetes.* There is habituation in respect of quinine, for which reason it is administered for eight consecutive days only, with intersecting intervals of eight days *Calcium ions* in large doses (6—8 gm of calcium gluconate daily) may accentuate the quinine effect. Quinine treatment is indicated only in cases where myotonia hampers working ability; this is mainly the case in patients with Thomsen's disease. Only in rare cases of dystrophia myotonica is there sufficient indication for quinine treatment.

Attempts at treatment *of muscle dystrophies* in patients with dystrophia myotonica have yielded no convincing results

At first glycine treatment, as applied against progressive muscle dystrophy, was *brought into use*, but *without definite effect* [*Slauck* (1933), *Waring, Ravin & Walker* (1940), and *Franceschetti* (1942)] This treatment was also attempted in one of my patients (No 86) — without effect

During recent years *vitamin E* treatment has been attempted *Franceschetti* (1942) and *Mongillo & Serog* (1944) reported that after such treatments their patients subjectively felt better, but objectively there were no demonstrable effects Vitamin E treatment has not been applied to any of the patients in this writer's material

Hormone treatments with thyroid hormone, testicular hormone, anterior pituitary, and cortiadrenal hormone preparations have been attempted in a few cases

Thyroid extract was applied by *Brock & Kay* (1920), *Weiss & Kennedy* (1924), and by *Waring, Ravin & Walker* (1940) without beneficient effect Powerful thyroidin treatment was attempted in respect of my patient No 28 To begin with she grew a little livelier, but later turned nervous and felt no improvement of muscle strength or other symptoms and treatment had to be discontinued

Testosterone may in animals produce muscle hypertrophy and increased activity [*Pedersen-Bjergaard & Bollerup-Madsen* (1938), *Lippros* (1938), and *Papanicolaou & Falk* (1940)] *Hesser, Langworthy & Vest* (1940) reported improved muscle strength in patients with dystrophia myotonica and gonadal dystrophy when treated with testosterone, and *Slauck* (1933) and *Mongillo & Serog* (1944) described subjectively felt improvement following the administration of testosterone propionate in connexion with glycine and vitamin E *Waring, Ravin & Walker* (1940), however, registered only a

very doubtful subjective effect of testosterone propionate treatment with and without simultaneous administration of glycine, and one of my patients (No 24) received testosterone preparations without definite effect

Anterior pituitary preparations have been applied in only a couple of cases [*Kolb, Harvey & Whitehill* (1937) and *Waring, Ravin & Walker* (1940] The latter patient felt subjectively improved after a very long period of treatment One of my patients (No 24) received gonadotropic chorionic hormone preparations (Physex) in comparatively heavy doses for several months, but no definite effect could be ascertained Nor was there any definite effect of simultaneous treatment with testosterone and gonadotropic chorionic hormone preparations

Cortiadrenal preparations have previously been applied against progressive muscle dystrophy [*Hartman, Beck & Thorn* (1933) and *Mendelson* (1934)] with somewhat doubtful effect *Kolb, Harvey & Whitehill* (1940) treated a patient, suffering from dystrophia myotonica, in this manner, but without effect I have in my material applied desoxycorticosterone acetate in doses of 10 mg every other day, in all 10 to 15 intramuscular injections, all three patients (Nos 82, 86, and 175) subjectively felt improvement of muscle fatigue In No 86 the force was measured by dynamometer before and during treatment There was definite increased strength of hand grasp, and the patient was nov able to get up, whereas before treatment she was unable to stay out of bed No 175 felt stronger and and put on ten lbs in connexion with the treatment

Cataract can be treated only when mature, and there is no way of arresting its development.

Reduction of B M.R may be counteracted through thyroidin treatment, which, however, gives no clear improvement of the condition; in general, thyroidin treatment should not be employed

Gonadal dystrophy with reduced sexual libido in males has been treated with testosterone preparations, but without definite effect on sexual potency and libido. The reported effect on muscle strength is not definite to such a degree that the application of testosterone preparations is advisable.

Menstruation disturbances have in certain cases necessitated endometrectomy, and in a single case profuse menorrhagia called for roentgen castration Hitherto, estrin has not been applied in these cases.

Nor are gonadotropic chorionic hormones of definite effect, but strong anterior pituitary preparations administered to young patients may possibly arrest non-muscular dystrophies in their development.

Cortiadrenal preparations (desoxycorticosterone acetate) subjectively in a number of cases caused improvement, and, objectively, in one single case improvement of muscle strength besides Muscle fatigue diminished, and this is likely to be a case of substitution therapy which should in future be applied more widely to debilitated patients with dystrophia myotonica

As will be seen from the present survey there is no known definitely efficient remedy for dystrophia myotonica

CHAPTER IX

THERAPY

Treatment *of the symptom myotonia* has already been dealt with in the chapter on that affection *Quinine* in large doses (1—1.75 gm. daily) is of a brief beneficial effect in the same manner as is insulin in diabetes. There is habituation in respect of quinine, for which reason it is administered for eight consecutive days only, with intersecting intervals of eight days. *Calcium ions* in large doses (6—8 gm of calcium gluconate daily) may accentuate the quinine effect. Quinine treatment is indicated only in cases where myotonia hampers working ability; this is mainly the case in patients with Thomsen's disease. Only in rare cases of dystrophia myotonica is there sufficient indication for quinine treatment.

Attempts at treatment *of muscle dystrophies* in patients with dystrophia myotonica have yielded no convincing results

At first glycine treatment, as applied against progressive muscle dystrophy, was brought into use, but without definite effect [*Slauck* (1933), *Waring, Ravin & Walker* (1940), and *Franceschetti* (1942)] This treatment was also attempted in one of my patients (No 86) — without effect

During recent years *vitamin E* treatment has been attempted *Franceschetti* (1942) and *Mongillo & Serog* (1944) reported that after such treatments their patients subjectively felt better, but objectively there were no demonstrable effects Vitamin E treatment has not been applied to any of the patients in this writer's material

Hormone treatments with thyroid hormone, testicular hormone, anterior pituitary, and cortiadrenal hormone preparations have been attempted in a few cases

Thyroid extract was applied by *Brock & Kay* (1920), *Weiss & Kennedy* (1924), and by *Waring, Ravin & Walker* (1940) without beneficient effect Powerful thyroidin treatment was attempted in respect of my patient No 28 To begin with she grew a little livelier, but later turned nervous and felt no improvement of muscle strength or other symptoms and treatment had to be discontinued

Testosterone may in animals produce muscle hypertrophy and increased activity [*Pedersen-Bjergaard & Bollerup-Madsen* (1938), *Lippros* (1938), and *Papanicolaou & Falk* (1940)] *Hesser, Langworthy & Vest* (1940) reported improved muscle strength in patients with dystrophia myotonica and gonadal dystrophy when treated with testosterone, and *Slauck* (1933) and *Mongillo & Serog* (1944) described subjectively felt improvement following the administration of testosterone propionate in connexion with glycine and vitamin E *Waring, Ravin & Walker* (1940), however, registered only a

CHAPTER X

EUGENICS

Patients with Thomsen's disease, paramyotonia, and dystrophia myotonica are registered at The University Institute for Human Genetics, Copenhagen; here is gathered all information obtainable concerning the patients and their families

Thomsen's disease and paramyotonia are comparatively benign diseases, requiring no special eugenic measures

Dystrophia myotonica, on the other hand, is an extremely serious affection — for the diseased individual, who will become invalided, and for the community, which will be called upon to aid the patient In this disease efficient eugenic precautions are indicated

Eugenic measures to be considered are sterilization of patients and recognized genetic carriers, provided they have retained their sexual potency. Sufficient in many cases will be to discourage the parties to a marriage, one of whom is a carrier, from having children Should pregnancy occur, induced abortion must be advised on eugenic grounds.

SOCIAL SECURITY AID

As already stated, none of this writer's patients with Thomsen's disease were hampered in their working ability to a degree that called for public relief.

About two thirds of the adult patients with dystrophia myotonica were so hampered as to be considered severely invalided. A considerable proportion of these patients receive invalidity pension, their working ability being less than one third, and a few live on subsidies from their families or on their own resources. Finally, the psychic changes in a number of patients are so severe that they are under care as mental defectives.

Although there is no available efficient remedy for treating dystrophia myotonica, it would be of help to these patients if the nature of their affection be recognized; for it would then be possible to provide the required aid through social welfare organizations.

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CHAPTER XI

SUMMARY

Chapter I (Introduction).

Myotonia was first described as a specific symptom in 1876 by the physician Asmus Julius Thomas Thomsen, who himself suffered from the ailment Myotonia is the characteristic symptom of the following hereditary affections Thomsen's disease (myotonia *congenita*), *para-myotonia, and dystrophia myotonica. These diseases, and particularly dystrophia myotonica, are not rare, and the question whether they may justifiably be considered separate nosological entities has been the subject of discussion. The problem is interesting, not only theoretically, but equally so from its practical aspect, especially with a view to eugenics.*

Chapter II.

The symptom *myotonia* appears *in the form* of an *involuntarily pro-tracted contraction of striated musculature, caused by voluntary inner-vation (active myotonia), mechanical stimulation (mechanical myotonia), or electrical stimulation of the muscle (electrical myotonia), and accom-panied by characteristic electrical phenomena in the musculature.*

In Thomsen's disease (and paramyotonia) *myotonia is most often* extremely widely spread and manifests itself in early childhood. In dystrophia myotonica, on the other hand, *it is generally localized in* single muscle groups (*muscles of forearms and mastication*), and very rarely becomes manifest before the age of 6, most frequently between the ages of 15 and 20.

Completely relaxed, myotonic muscles are of normal consistency, and their tone is normal. The *myotonia to a certain extent is dependent on the exertion of strength, and decreases upon repetition of contraction* In the majority of cases the functional hampering is most strongly felt in cold, albeit the myotonic phase is shorter. Fatigue and mental affect-ions, menstruation, and pregnancy *may aggravate myotonia In severe* cases the patient, when *frightened, may become rigid as a statue for about one minute*

In Thomsen's disease myotonia may seemingly grow less of an inconvenience with growing age. In dystrophia myotonica, myotonia disappears with the appearance of dystrophy in the muscle.

Mechanical myotonia must not be confused with idiomuscular reaction, which appears as a local protuberance, whereas the mechanical myotonia most often appears as a furrow on the surface of the muscle corresponding to the contracted fasciculus Its distribution almost corresponds to that of active myotonia and is particularly clearly demonstrated on the edge of the tongue, in forearm extensors and thenar. Electrical myotonia has not been investigated in the present work.

Myotonia has been demonstrated in a certain breed of goats from Tennessee, U.S A These animals have been used in patho-physiologic and pharmacological experiments

Electromyography with concentric needle electrodes constitutes an extremely important method of examination in respect of myotonia. Myotonia is accompanied by a characteristic electrical activity, and in the resting myotonic muscles may generally be demonstrated a typical activity

The specific myotonic electrical activity, as far as can be judged, originates from the muscle plate, which must be abnormally sensitive, as it reacts to voluntary innervation and mechanical and electrical stimulation, not — as a normal muscle plate — with a single, but with a series of oscillations. This myotonic activity disappears upon local application of *one half per cent novocaine solutions and upon local and universal treatment* with quinine

There has not been demonstrated any difference between the myotonia in patients with Thomsen's disease as compared with dystrophia myotonica.

Myotonia may be made to disappear partly or wholly through treatment with heavy doses of quinine (1—1 75 gm daily by mouth) The effect is short and can be accentuated by large doses of calcium. There is habituation, for which reason quinine treatment is administered for eight consecutive days, with intervals of eight days The treatment is generally indicated only in Thomsen's disease, rarely in dystrophia myotonica

Chapter III

There are only muscular symptoms in *Thomsen's disease*. generally extremely widespread myotonia and, in the majority of cases, more or less pronounced muscular hypertrophy, never dystrophy. Strength not always corresponds to volume of muscles. Non-muscular dystrophies, so characteristic of dystrophia myotonica, are never found, and the social

level of the patients is not affected by the disease. None of this writer's 29 patients needs social security aid on account of Thomsen's disease.

The disease is not nearly so frequent as dystrophia myotonica It has been reported in many European countries, in the U. S A , and in Japan, and there is no demonstrable relation between the families reported. Its appearance is equally frequent in males and females, but males form the majority of propositi It most often manifests itself in early childhood and in some cases is present in infancy. It is hereditary. In Dr. Thomsen's family and in a number of others its inheritance is simply dominant with strong penetration, whereas in other families it is presumably inherited dominantly with varying manifestation. The possibility in certain families of recessive heredity cannot with certainty be excluded.

The clinical and genetic aspects of the disease are illustrated in the present work through investigation of five Danish families (including one branch of Dr Thomsen's family) with 29 living patients.

Chapter IV.

Paramyotonia appears in the form of spontaneous, tonic contraction in striated muscles, followed by more or less pronounced paresis caused by cold temperatures From the cold-phenomena in myotonia there is a gradual transition to paramyotonia; and as there is practically always muscle hypertrophy in patients with paramyotonia, the syndrome paramyotonia is considered a special variant of Thomsen's disease Heredity is dominant

There are no patients with paramyotonia in the present material.

Chapter V

A critical survey of the literature on *myotonia acquisita* tends to demonstrate that this diagnosis is probably without justification.

Chapter VI

In certain patients with *myxedema* there is muscle hypertrophy and tardy muscle functioning (*Debré-Semelaigne's* syndrome) and in others, besides, a myotonoid functional disturbance (*Hoffmann's* syndrome). This latter syndrome has frequently been reported as Thomsen's disease. Investigations of a patient with this syndrome reveal that myotonia is out of the question Muscle hypertrophy and myotonoid functional disturbances yielded, together with myxedema, to thyroidin treatment.

Chapter VII.

Dystrophia myotonica is first and foremost marked by dystrophic symptoms, partly muscular, and partly non-muscular. The myotonia is most often localized in single symmetrical muscle groups and particularly in the finger flexors. Muscle dystrophy mainly affects muscles of face, mastication, tongue, neck, and forearms, but may gradually become very widely spread. There are no characteristic changes in creatine-creatinine excretion in the urine. As a rule the reflexes are weakened in dystrophic muscles, but this phenomenon may also be ascertained in muscles not so affected. In rare cases slight hypesthesia and hypalgesia was ascertained distally in the extremities, and impaired sensitiveness to vibration has been reported in a number of patients (Maas)

Cataract is frequently found as a solitary symptom in the parents of the patients In 87 per cent of this writer's patients were found lenticular opacities, which in the majority of cases were of comparatively characteristic appearance (cataract in myotonia) Cataract rarely becomes mature before the age of 45 Ptosis, lagophthalmos, and blepharoconjunctivitis are caused by muscle dystrophy, but the fairly constantly appearing enophthalmos may be of endocrine origin

Gonadal dystrophy was found in 86 per cent of the males and presumably in 64 per cent of the females, who had menstruation disturbancies. In the majority was ascertained decreased excretion of testicular hormone and estrin, and reduced sexual libido and potency

Reduced B. M R without myxedematous symptoms was found in many patients Most often the thyroid gland had colloidal changes.

There were no definite changes in the internal secretion of the pancreas, although the blood sugar level was often a little low

There is no special clinical basis for the assumption of dystrophy of the cortex of the suprarenal gland ascertained through histological investigation Attempts at substitution therapy resulted in three cases in subjective improvement of fatigue

The functioning of the parathyroid glands was seemingly normal

The clinical picture in dystrophia myotonica has certain points in common with the chronic form of Simmond's syndrome, and although definite changes have not yet been ascertained through histological investigations, the variegated clinical picture may, in all likelihood, be referred to functional disturbances in the hypothalamos-hypophysis system.

Frontoparietal baldness together with the typical myopathic facies endows the patients with a characteristic appearance. Alopecia was found in 83 per cent of the males, but in only 16 per cent of the females.

Vasomotor disturbances with acrocyanosis and vasospasms were established in two thirds of the patients, and at electrocardiography the

conduction was in some cases prolonged. Reports have appeared of passing heart block, and many patients have slight bradycardia.

Very frequent symptoms are deformations of the facial skeleton with high palate and adenoid appearance. Forward-drooping head, accentuated curvations of the back, recurvation of knees, and talipes equinus are extremely frequent features. In a few cases was demonstrated thickening of the theca cranii and internal frontal hyperostosis.

Mental changes form a very important symptom Intellectual deterioration to a considerable degree is found in one third, and reduced initiative in three fifths, of patients in the working age groups. Several are taken care of in hospitals for mental defectives. The mental changes in many cases constitute a further drawback in the already reduced working ability of these patients.

Definite social deterioration is almost invariably found in patients with dystrophia myotonica The working ability is less than one third in 61 5 per cent of patients between 15 and 60, and many receive invalidity pension.

The affection is spread over Europe, the U. S A., South America, and Japan, and is far more frequent of occurrence than Thomsen's disease. It is found equally often in males and females, but muscle dystrophy, like social deterioration, is generally most pronounced in males. The average age of manifestation of this disease is 19 years, at later manifestation the symptoms are often weaker The majority die before the age of 50.

Effective fertility is reduced, and a strikingly high proportion of the patients are unmarried The disease is inherited dominantly with varying never failing manifestation Certain factors support the view that the heredity is progressive, ending up with diseased individuals without power of propagation, but the progression is possibly due to selection in the parents' generations. Fraternal degeneration was found in none of this writer's families The investigation covers 21 families with 101 living patients

Chapter VIII

Clinical investigations have revealed that Thomsen's disease (and
aramyotonia) are different in nature from dystrophia myotonica The
mily investigations have yielded no basis for the theory advanced by
her authors· that genetically these affections are identical.

Recognition of the myotonic symptom facilitates diagnosis in contra-
tinction to a number of muscle affections and diseases with symptoms
esponding to the non-muscular dystrophic changes in dystrophia
tonica. A handshake will often be sufficient to reveal the true diag-
s.

Chapter IX

The symptom of myotonia may be treated with quinine, but such treatment is generally indicated only in respect of patients with Thomsen's disease

A thoroughly effective therapy in dystrophia myotonica is unknown, but desoxycorticosterone acetate may in certain cases have a beneficient effect on the asthenia which inconveniences many of these patients. Vitamin E in large doses may possibly arrest the development of muscle dystrophy, but up to the present, improvements have been only subjective.

Recognition of the disease will be of help to many patients, for in this manner it is possible to provide for them the necessary social security aid

Chapter X

Eugenic measures come into consideration only in dystrophia myotonica Thomsen's disease (and paramyotonia) may well be an inconvenience, but rarely a disability Patients with, and definite genetic carriers of, dystrophia myotonica will first be advised not to have children and taught the required measures Should this prove insufficient it is possible that resort must be taken to sterilization and induced abortion on eugenic grounds

CHAPTER XII

CASE HISTORIES

The investigation reported comprises 21 families with dystrophia myotonica, the families having 1,148 members, 874 of whom are living. Among those living 101 were certain cases of dystrophia myotonica, and 4 had not quite certain symptoms of the disease. 17 had cataractous changes without muscular symptoms. Among those dead, 44 had symptoms indicating dystrophia myotonica, and 14 had had manifest cataract Finally, there are 2 family members with schizophrenia. One is living and presents no symptoms of dystrophia myotonica; the other is dead and no further information is available.

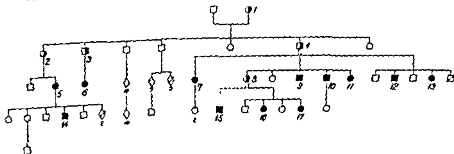
Case histories are reported only in respect of actually or supposedly affected family members, enumeration shows their position in the pedigrees. By way of introduction to the case histories of each family I have briefly reported the history of the family and its social conditions.

The reported case histories are very brief, but complete case records are to be found in The University Institute for Human Genetics, Copenhagen.

Family No 1

The family can be traced back through five generations to the family of a smallholder, born c 1838 The majority of family members have lived and still live in the central part of the Djursland district, Jutland Their social level is that of small-holders and unskilled labourers. The investigation covers 70 persons, of whom 56 are living

Among those living, 10 have dystrophia myotonica and 3 have cataractous changes Among the dead, 2 are supposed to have had dystrophia myotonica and 2 had cataract The disease of the propositus was recognized by *Haagen Jessen*, Aarhus



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aks (s l e)

5. a myotonica

of 25 Cataract from age of 44 — Typical *myotonia* and severe muscle dystrophy with myopathic facies and dropfoot Severe *mental* changes marking appearance of her home Is extremely *weakened and tired Hypermenorrhea medium-sized struma, and acrocyanosis*

6.

7.

8

cortex single green points (s l e)

9 Male, s, former unskilled labourer aged 35 *Dystrophia myotonica Propositus*
Mentally debilitated from childhood from age of 20 weakening of muscles and myotonia Was always a bad worker unable to work from age of 28 Typical myotonia and comparatively severe muscle dystrophy with myopathic facies Atrophy of *testes (left testis removed by operation) Alopecia and acrocyanosis* Slight, emaciated appearance miserable Bad social conditions receives invalidity pension

10 Male, m, former unskilled labourer aged 32 *Dystrophia myotonica*
Myotonia and muscle debilitation from age of 21 — *Typical myotonia* and *comparatively* severe muscle dystrophy especially in arms *Slight mental changes* Severe acrocyanosis Cataract *with few* dust-formed, some of them red-coloured, subcortical grains (s l e) Comparatively strongly built appearance marked only slightly by the disease Rather bad social conditions Receives invalidity *pension*

11 Girl, d aged 15 *Supposed dystrophia myotonica*

12 Male, s, farm hand, aged 25 *Dystrophia myotonica*
Myotonia and debilitation of arm muscles from age of 12 Works comparatively well, but at reduced wages Typical *myotonia* and slight muscle dystrophy with myopathic *facies* Atrophy of testes and genitalia Social conditions comparatively good

13 Female, s, domestic servant aged *21 Dystrophia myotonica*
Myotonia and debilitation of muscles from age of 14 Has always been mentally debilitated and never
dystrophy with myop
rhea Cataract *with p*
Lives on *her family*

14 Male s, former farr
Myotonia and g
permanent work –
facies Severe menta
bad, receives invalidity pension

15 Male, s, former farm hand, aged 22 *Dystrophia myotonica*
Myotonia and debilitated muscle strength of hands from age of 14 Mentally debilitated from childhood has never had permanent work — Typical myotonia and slight muscle dystrophy with myopathic facies Severe mental changes atrophy of testes and genitalia Acrocyanosis Cataract with greyish and brownish subcapsular anterior and posterior points with faint stellate formation in left lens (s l e) Lives on his family *Bad social* conditions receives invalidity pension

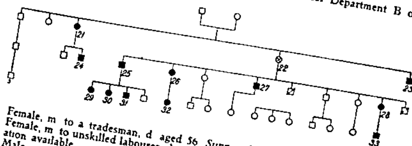
16 aged 14 *Dystrophia myotonica*
n early
ty with
ls, and
which
are green (s l e)

Family No. 3

This family can be followed through four generations to a family of small-holders from about 1838, living between Roskilde and Copenhagen The present members live somewhat scattered, and the majority have belonged to the class of unskilled labourers Only a few living members are clerks The investigation comprises 37 persons, 28 of whom are living

Of these 28, 9 have dystrophia myotonica, and 3 of the dead had symptoms of the disease

The disease of the propositus was recognized in Medical Department B of the Rigshospital, Copenhagen



21 Female, m to a tradesman, d aged 56 *Supposed dystrophia myotonica*

22 Female, m to unskilled labourer, d aged 62 Had schizophrenia No further information available

23 Male, s, unskilled labourer, d aged 47 *Supposed dystrophia myotonica*
Was lazy, addicted to drink, and dromomanic had dropfoot Photograph shows myopathic facies

24 Male, s, clerk, aged 39 *Dystrophia myotonica*
Increasing muscle debilitation from age of 18 When 16 treated for achylia When 37, treated for Simmond's syndrome Is employed on light work — Typical myotonia and slight muscle dystrophy with myopathic facies, very slack and tired Extremely emaciated and nasal speech Mentally somewhat changed, B M R 74—68 per cent, serum cholesterol 260 mg per cent blood sugar when fasting 069 — 083 per cent Ecg natural B P 100/50 Astrophy of testes and external genitalia Hormone excretion in urine gonadotropin normal, testicular hormone 2 H U (normal 5—25), and estrin normal Is alopecic and has acrocyanosis Slight cataract with subcortical dust-formed opacities (s l e) In the Medical Out-Patient Dept of the Rigshospital he has received treatment with gonadotropic chorionic hormone and testosterone acetate without effect Social conditions comparatively good

25 Male, m, unskilled labourer d aged 35 *Supposed dystrophia myotonica*
Had myotonia and was very debilitated during his last years

26 Female, m to unskilled labourer aged 44 *Dystrophia myotonica*
Myotonia and muscle debilitation from age of 26 Despite feeble strength she manages to look after her home — Typical myotonia with myopathic facies, nasal speech, paralytic coughing and very weak arm muscles Slight mental changes The patient is terribly emaciated and very slack and tired Hypomenorrhea for many years, menopause at 41 Incipient alopecia, acrocyanosis and cataract with incipient stellate formation in posterior cortex and fine, coloured grains in anterior cortex (s l e) Social conditions comparatively bad

27 Male, m, unskilled labourer, aged 40 *Dystrophia myotonica*
At 30 myotonia and increasing muscle debilitation From 36 unable to work Has been imprisoned for procuring Typical myotonia and extremely severe muscle dystrophy with extremely severe paresis of shoulder and upper arm muscles, so that his arms hang slack like those of a doll Light mental changes, alopecia and acrocyanosis Social conditions very bad receives regular sick allowance Has one child in wedlock, and is stated to be the father of three other children, but his paternity in respect of the latter is very doubtful

28 Female, divorced from driver aged 35 *Dystrophia myotonica Proposita*
From childhood slept with eyes open Growing muscle debilitation and fatigue

pension

29 Female, s , domestic servant, aged 22 *Dystrophia myotonica*
Myotonia and acrocyanosis from age of 10 — Typical myotonia and slight muscle dystrophy and slight myopathic facies Mentally normal Comparatively good social conditions

30 Female, s , domestic servant, aged 20 *Dystrophia myotonica*

31

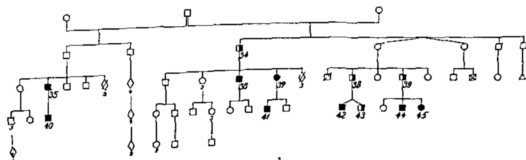
32

vegetation removed on account of changed speech and appearance Has never been able to perform paid work — Typical myotonia and extremely severe muscle dystro-

33

Family No 4

This family has been followed through five generations to a small-holder, b 1815 He married twice, and dystrophia myotonica appears in both families The family first lived in the region north of Horsens, Jutland, and the majority belong to the unskilled labouring group; a few have, however, broken away as artisans and a single member



is a teacher The family members now live scattered in Jutland and in Copenhagen. The investigation covers 82 persons, 55 of whom are living in this country

Of those living, 7 have dystrophia myotonica and 3 have cataract Among the dead there is one supposed case of dystrophia myotonica and one of cataract

The myotonia in the propositus was recognized in the Neurological Department of the Kommunehospital, Copenhagen Dystrophia myotonica was recognized in 1938 by this writer in the Orthopedic Hospital, Copenhagen

34 Male, m, blacksmith, d aged 80 *Cataract*

35. Male, m, unskilled labourer, d aged 43 *Supposed dystrophia myotonica*
Had myotonia and weak muscles Photograph shows myopathic facies

36 Male, m, unskilled labourer, aged 56 *Dystrophia myotonica*
Growing muscle debilitation from age of 20 Myotonia from age of 40 Unable to work from age of 48 Receives invalidity pension on diagnosis progressive spinal muscular atrophy (Duchenne-Aran type) -- Typical myotonia and extremely severe dystrophy with myopathic facies nasal speech and very weak strength of both arms and legs Severe mental changes Atrophy of testes and external genitalia Alopecia Very emaciated and of miserable appearance Cataract Social conditions bad

37 Female, m to unskilled labourer aged 46 *Dystrophia myotonica*
Myotonia and cold-sensation in hands from age of 10 Slack and weak of muscles from age of 14 — Typical myotonia and slight muscle dystrophy Very pronounced lack of initiative that leaves its marks on the home to an unpleasant degree Further, slight intellectual deficiency Cataract with partly peripheral larger or smaller opacities, and, partly, numerous point-formed opalescent opacities with posterior stellate formation (s l e) Acrocyanosis The patient lives under very bad social conditions and receives invalidity pension

38 Male, m, mechanic, aged 52 *Cataract*
Manifest from age of 47 and operated on right eye In left eye numerous small metal-shining opacities and stellate formation in posterior cortex (s l e)

39 Male, m, carver, aged 47 *Cataract*
Anteriorly and posteriorly, fine metal-shining subcapsular opacities and cloud-like stellate formation (s l e)

40 Male, s, unskilled labourer, aged 37 *Dystrophia myotonica*
Myotonia and growing muscle debilitation from age of 14 Has never had permanent work and has not worked from age of 17 Sponges on his old mother — Typical myotonia and slight muscle dystrophy with myopathic facies and nasal speech Comparatively severe mental changes Atrophy of testes and external genitalia Alopecia and acrocyanosis Social conditions are bad, following this writer's examination he receives invalidity pension

41 Male, s, inmate of an institution, aged 20 *Dystrophia myotonica*
Myotonia and increasing muscle debilitation from age of 8 Mentally debilitated from early childhood, admitted to a home for backward persons — Typical myotonia and slight muscle dystrophy with slight myopathic facies Atrophy of testes acrocyanosis, and cataract with numerous, partly opalescent opacities with incipient stellate formation (s l e) Social conditions bad, is under public care

42 Male, s, former journeyman painter, aged 22 *Dystrophia myotonica Propositus*
Typical myotonia and considerable development of muscles from age of 10 Increasing muscle dystrophy with typical localization from age of 18 Had difficulty in carrying through his term of apprenticeship as a painter has been incapable of working at his trade — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies, dystrophy of neck muscles and weak hand-grasp Comparatively severe mental changes with pronounced lack of initiative Alopecia, acrocyanosis, and cataract with incipient stellate formation and point-formed crystalline opacities in the posterior cortex (s l e) Rather bad social conditions, he now receives invalidity pension Is a twin but does not resemble his brother (43)

43 Male, s, baker, aged 22 *Cataract*
Suspicion of radial streaky opacity and small white opacities in the posterior cortex

44 Male, s, messenger, aged 20 *Dystrophia myotonica* Fig 10
Myotonia and increasing debilitation of muscles from age of 9 Was unfit for training as an artisan Works at low wages as a messenger — Typical myotonia

and comparatively slight muscle dystrophy with myopathic facies. In legs, muscle hypertrophy Comparatively severe mental changes. Atrophy of testes B.M.R. 95 per cent Slight acrocyanosis Lives with his parents, social conditions bad. Receives

45.

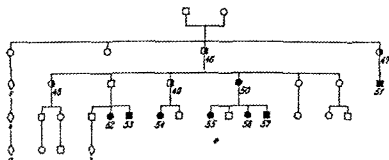
Myotonia
rwise no
number

Family No. 5.

The family can be traced five generations back to the family of a farmer, b. 1797 and living on a family farm north of Birkerod, Zealand Their descendants are mainly farmers, and some are unskilled labourers They chiefly live in the same region The investigation comprises 59 persons, 45 of whom are living.

Among those living there are 6 cases of dystrophia myotonica and one of cataract, whereas among the dead there are 2 supposed cases of dystrophia myotonica and 3 of cataract

The disease of the proposita was recognized in 1936 by *Georg K. Sturup* in the Orthopedic Hospital, Copenhagen



46 Male, m., farmer, d. aged 75 *Cataract*
47 Female, m to house-owner, d. aged 50 *Cataract*
48 Female, m to unskilled labourer, d aged 70 *Cataract*
49 Male, m., farmer aged 69 *Cataract*
50 Female, m. to house-owner, aged 64 *Dystrophia myotonica*
Cataract from age of 51 — Mechanical myotonia in typical sites only, and extremely slight muscle dystrophy with myopathic facies. Mentally normal Slight acrocyanosis Social conditions good
51 Male, m., unskilled labourer, d aged 69 *Supposed dystrophia myotonica*
Was mentally debilitated and had weakness of muscles of the same nature as in patient No 53

52

53

others, but a little ... severe dystrophy of neck muscles, and especially dystrophy with myopathic facies,

54

s of lower extremities
se hyperostosis B. P.
social conditions bad

55

56.

fairly good

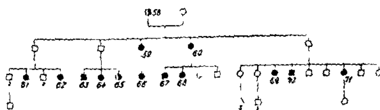
57. Male, s., messenger, aged 23 *Dystrophia myotonica*
Myotonia and acrocyanosis from age of 13 Mentally debilitated from childhood; later under care as mentally deficient — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies Imbecility and considerable reduction of initiative Atrophy of testes and incipient alopecia Acrocyanosis and cataract with fine thread-formed opacities emanating from the suture lines Further, single green grains (s l e) Social conditions bad Is under care in a private family as mentally deficient

Family No 6

It is possible to follow this family through four generations to the family of a small-holder, b about 1839, living between the towns of Herning and Ringkobing, Jutland Their descendants were unskilled labourers small-holders, or civil servants of lower rank Some of their living descendants are artisans or clerks They partly live in the same region as their ancestors, partly in Copenhagen The investigation comprises 44 persons, of whom 32 are living

Of these 32, 7 have dystrophia myotonica and one cataract Dystrophia myotonica is supposed to have been present in 5 of the dead and one was possibly a case of cataract

Eigil Hess-Thaysen, in the Medical Department of the Herning Sygehus, Jutland, recognized the disease in the propositus



58 Male, m., small-holder d at unknown age *Possibly cataract*
59 Female, s., housekeeper d aged 62 *Cataract and supposed dystrophia myotonica*
60 [illegible]
61

cyanosis Social conditions bad

62. Female, s., do[illegible]
Myotonia [illegible]
venienced by [illegible]
from childhoo[illegible]
severe muscle dystrophy with myopathic facies, nasal speech, and weak strength of arms and hands Severe mental changes. Hypermenorrhea and metrorrhagia Histological diagnosis irregular endometrial hyperplasia Hormone excretion in urine· gonadotropin, normal; testicular hormone· 1 H U. (normal, 5—25); and estrin 8 M U (normal 20—150) Acrocyanosis and cataract with stellate formation and metal-shining point-formed opacities in the posterior cortex (s l e). Appearance extremely miserable and pitiable. Very bad social conditions, lives with helpful strangers Receives invalidity pension

63 Male, s, former clerk, aged 44. *Dystrophia myotonica*
Myotonia from age of 36. Severe myopia from childhood Has not worked [illegible]

sisters Social conditions bad, he now receives invalidity pension

64 Female, s., book-keeper, aged 38 *Dystrophia myotonica*
Slight myotonia, especially in cold, from age of 30 Never inconvenienced in her work. Very slight myotonia in hands, and very slight dystrophy in face and neck. No mental changes *Cataract with point-formed opacities in anterior as well as posterior cortex*, and more diffuse radial subcapsular opacities (s l e). Social conditions good

65 Female, s., shop assistant, aged 37 *Cataract*
Juvenile cataract with cortical as well as nuclear heterogeneous opacities of varying shape and colour (s l e)

66 Female, s, domestic servant, d aged 21. *Supposed dystrophia myotonica*

67 Male, s, brush-maker, aged 43 *Dystrophia myotonica*
[illegible]

pension

68 Female, s, domestic servant, d aged 24 *Supposed dystrophia myotonica*

69 Female, s, housekeeper, aged 41 *Dystrophia myotonica*
From age of 15 myotonia, aggravated at menstruation Increasing fatigue with growing age Difficulty in managing light housework. — Typical myotonia and slight muscle dystrophy with myopathic facies and nasal speech Severe mental changes Corpulence and cataract with speck- and dust-formed opacities besides cerulean changes (s l. e) Lives under comparatively bad social conditions without public aid

70 Male, s, farm-hand, aged 38 *Dystrophia myotonica Propositus*
Myotonia and increasing muscle debilitation from age of 23 Unable to work [illegible]
[illegible] *pnos-*
[illegible] urine:
[illegible] estrin
[illegible] yotonia
[illegible] ianged
[illegible] is bad
[illegible]
Receives invalidity pension

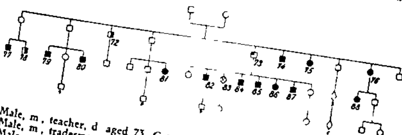
71 Female, m to farmer, d, aged 31 *Supposed dystrophia myotonica.*

Family No 7

The family can be traced back through four generations to a family of farmers, b 1829—1831, living on a farm which is still possessed by the family It is situated in the central part of the Djursland region Jutland Their descendants are mainly farmers, but there are some tradesmen a single teacher, and some unskilled labourers Social deterioration is clearly evident as soon as dystrophia myotonica appears The investigation covers 49 persons, 34 of whom are living

Of those living there are 9 cases of dystrophia myotonica and one of schizophrenia without muscular symptoms Among the dead there are 5 supposed and one suspected, cases of dystrophia myotonica, and one family member in the U S A has supposed cataract.

The disease of the proposita was recognized in the Neurological Department of the Kommunehospital, Copenhagen



72 Male, m, teacher, d aged 73 *Cataract and supposed dystrophia myotonica*
73 Male, m, tradesman, d aged 61 *Suspected dystrophia myotonica*
74 Male, m, farmer, d aged 68 *Supposed dystrophia myotonica*
75 Female, s, d aged 65 *Supposed dystrophia myotonica*
76 Female, m to former farmer a 72 *Dystrophia myotonica*
Cataract and increasing physical and mental debilitation from age of 57 Very slight myotonia and muscle dystrophy with nasal speech Comparatively severe mental changes Incipient alopecia and cataract Fairly good social conditions
77 Male, m, workman, d aged 55 *Supposed dystrophia myotonica*
78 Male, m, workman, d in the U S A *Possibly cataract*
79 Male, s, independent means, aged 49 *Dystrophia myotonica*
Myotonia and hypersensitiveness to cold in hands from age of 20 Always been mentally debilitated and never fit to work Has for many years led a spongin existence on the family farm — Typical myotonia and severe muscle dystroph especially in proximal parts of lower extremities Almost unable to walk Seve mental changes Atrophy of testes and external genitalia Obesity, acomia, an acrocyanosis Lives on his own means otherwise bad social conditions
80 Male s, former farm-hand aged 42 *Dystrophia myotonica*
Inceasing lack of strength in hands from age of 14 myotonia from age of 19 Has been unable to work for several years Lives with his brother (No 79) — Typical myotonia and extremely severe muscle dystrophy, especially in proximal muscles of extremities Can only with difficulty get up from a chair and walk Comparatively severe mental changes Atrophy of testes and external genitalia Alopecia and acrocyanosis He also lives on independent means Otherwise social conditions bad
81 Female, s, aged 48 *Dystrophia myotonica*
Myotonia from age of 6, and severe imbecility from early childhood -- Typical myotonia and very slight muscle dystrophy Severe intellectual deficiency Menopause at 32 Lives with her family and receives invalidity pension
82 Male, m, former commercial traveller aged 49 *Dystrophia myotonica*
Myotonia and increasing muscle debilitation from age of 23 During the last seven years so weak that he has been admitted to a municipal infirmary for nursing Not worked from his 25th year   Typical myotonia but slight on

account of extremely severe muscle dystrophy with myopathic facies and universal debilitation of muscles Unable to walk Comparatively severe mental changes Atrophic testes and external genitalia Horrifyingly emaciated, especially in the face Alopecia and acrocyanosis No cataract (s l e). Very bad social conditions, receives invalidity pension It is very doubtful whether he is the father of the wife's two sons who are both healthy.

83 Female, divorced from book-keeper, aged 46 *Schizophrenia*

84 Male, s, workman, d aged 22 *Supposed dystrophia myotonica*

85 Male, divorced commercial traveller, aged 43 *Dystrophia myotonica*

Myotonia, especially in cold, from age of 6 Cataract from age of 21 Operated on left eye — Typical myotonia and slight muscle dystrophy with generally thin muscles and pronounced muscle fatigue Mentally nearly normal Atrophy of testes and incipient alopecia Cataract in right eye with fine opalescent points in [illegible] to the centre (s l e). [illegible] mg every other day, [illegible] g of the fatigue Can [illegible] ons comparatively bad

86 [illegible] ica *Proposita*

Myotonia and muscle debilitation from age of [illegible] Especially inconvenienced by increasing muscle fatigue When 40 she [illegible]

[illegible] es, nasal speech, bad carriage, and diffuse reduction of strength in the extremities Slight mental changes, very touchy and unsociable B M R 100—105 per cent Ecg normal B P 110/50 Hormone excretion in urine gonadotropin > 30 R U (normal < 30); estrin normal Cataract with fine cortical changes in the posterior cortex with stellate formation Similar formations in the anterior cortex (s l e) Glycine treatment had no beneficient effect on strength reduction, whereas desoxycorticosterone acetate (Cortiron) 5 mg daily for about one month resulted in subjective improvement of muscle strength, and strength of hand-grasp went up from 4—5 kg to 10—15 kg Simultaneously the concentration of electrolytes in the blood serum rose from 148 to 152 mq (normal 155 mq) Together with Cortiron the patient for some time received insulin to stimulate her appetite Creatine and creatinine excretions were unchanged during treatment with glycine and Cortiron She has later repeatedly received Cortiron with definite improvement of strength. Appearance miserable, she is terribly emaciated Social conditions bad Receives invalidity pension

87. Male, s, mental defective, aged 39 *Dystrophia myotonica.*

Myotonia and increasing muscle debilitation from age of 32 Considerable degree of imbecility from childhood Admitted to mental asylum from his 17th year — Typical myotonia and very severe muscle dystrophy with myopathic facies, nasal speech, considerable reduction of strength, and paresis in lower extremities Walks with difficulty Imbecile, dirty habits as to faeces and urine, indecent towards younger patients Atrophy of testes and alopecia Repulsive appearance, emaciated and miserable Under care as mentally defective

88 Female, s, domestic servant, aged 46 *Dystrophia myotonica*

Myotonia, increasing muscle debilitation, and mental deterioration from age of 16 — Typical myotonia and comparatively severe muscle dystrophy with myopathic facies and nasal speech Severe mental changes Menopause when 40 Acrocyanosis Miserable appearance Lives on a healthy brother Bad social conditions

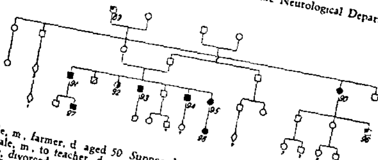
Family No. 8

The family can be followed through four generations to the family of a farmer, born c 1825, in a village between Bramminge and Kolding, Jutland Their descendants were and are small-holders or unskilled labourers, and a single member married a teacher The present generations live rather scattered, and their social level corresponds to that of their forefathers The investigation comprises 55 persons, 41 living

Dystrophia myotonica is present in 6 of the living members, and one has cataract

Of those dead, 2 are supposed to have had dystrophia myotonica and one is a suspected case

The disease of the propositus was recognized in the Neurological Department of the Rigshospital, Copenhagen



89 Male, m, farmer, d aged 50 *Supposed dystrophia myotonica*
90 Female, m, to teacher, d aged 76 *Supposed dystrophia myotonica*
91 Male, divorced unskilled labourer, aged 54 *Dystrophia myotonica*
Myotonia and increasing muscle debilitation from age of 40 After age of 46 employed on lighter casual work — Typical myotonia and stiffness in legs at initial steps Comparatively severe muscle dystrophy with myopathic facies, nasal speech, and bad carriage Moderate mental changes Atrophy of testes and external genitalia Alopecia and acrocyanosis Cataract with small-pointed opacities in the cortex, especially posteriorly Nucleus yellowish sclerotic (s l e) Bad social conditions, receives invalidity pension
92 Female, s, housekeeper, aged 50 *Cataract*
In left side angular subcapsular opacities of irregular size (s l e)
93 Male, m, unskilled labourer, aged 48 *Dystrophia myotonica Propositus*
Myotonia and increasing muscle debilitation in hands from age of 36 When 45, he was examined in the Medical Department with the conclusion that "the complaints of the patients were, in reality unfounded" — Comparatively spread myotonia and severe muscle dystrophy with myopathic facies nasal speech, and, further, diffuse dystrophy of all muscles in trunk and extremities Ecg normal P—Q 20 sec Blood sugar 074—096 Sugar tolerance graphs somewhat low rising slowly B P 75/45 Serum calcium and serum cholinesterase normal No cataract (s l e) The patient is excessively emaciated especially in the face Social conditions extremely bad Receives invalidity pension
94 Male, divorced unskilled labourer aged 43 *Dystrophia myotonica*
Myotonia and increasing muscle debilitation from age of 28 During recent years unable to work — Typical myotonia and slight muscle dystrophy with myopathic facies and slightly nasal speech Comparatively severe mental changes Atrophy of testes and external genitalia and incipient alopecia Has for several years led a vegetative existence, living on a brother Social conditions bad Receives invalidity pension Paternity of children a little doubtful
95 Female, m to mechanic, aged 41 *Dystrophia myotonica*
Very slight myotonia from age of 20 Received quinine against asthma and noticed beneficient effect on myotonia — Active myotonia in right hand and comparatively spread mechanical myotonia Extremely slight muscle dystrophy with slight myopathic facies Mentally natural Slight acrocyanosis and cataract with angular or streaky, yellowish-white, shining opacities of irregular size in the cortex (s l e) Home neat, social conditions good
96 Male, s, training college student d aged 20 *Suspected dystrophia myotonica*
97 Male s, messenger, aged 24 *Dystrophia myotonica*
Myotonia and muscle debilitation from age of 7 Mentally debilitated and always very tired and weak from childhood Attempted training in various trades, applied three times in vain for invalidity pension The authorities were of the opinion that he was lazy and lacked adequate training — Typical myotonia and comparatively severe muscle dystrophy with myopathic facies nasal speech and weak strength in the muscles of the extremities Severe mental changes Atrophy of testes and external genitalia Acrocyanosis and emaciation to a horrifying degree

especially in the face Social conditions bad Lives on his mother Now receives invalidity pension

98 Girl, daughter of mechanic, aged 14 *Dystrophia myotonica*
Myotonia of slight, but characteristic nature first observed at the family examination Exceedingly slight muscle dystrophy, especially in the neck Mentally natural No cataract (s l e)

Family No. 9.

The family has been followed through four generations to a woman, b 1841, living in the central part of the Djursland region, Jutland Prior to her marriage she had a child by a man, who has no other descendants. The descendants were and are unskilled labourers or small-holders, mainly domiciled on their native soil. The investigations comprises 49 persons, 35 of whom are living

Dystrophia myotonica is found in 11 of the 35 living members, and one is a suspected case Among the dead, one had cataract and one is suspected of having had dystrophia myotonica

The myotonia in the propositus was recognized by *Haagen Jessen*, Aarhus

99 [illegible]
100 [illegible]
101 [illegible]

[illegible] pension

102. Male, m. unskilled labourer, aged 47 *Dystrophia myotonica*
[illegible] Vision [illegible] h myo- [illegible] miser- [illegible] lighter [illegible] work Social conditions fairly good

103 Female, m to unskilled labourer, aged 45 *Dystrophia myotonica*
Myotonia and increasing loss of strength in hands from age of 14 Hands al- [illegible] very slight muscle dystro- [illegible] Severe mental changes, to [illegible] Cataract with fine coloured [illegible]

104 [illegible]

105 Male, m, unskilled labourer, aged 27 *Dystrophia myotonica*

Myotonia, increasing weakness and hypersensitivity to cold in hands from age of 10 Has difficulty in milking and carrying objects Quinine treatment — 1 gm daily — administered by *Haagen Jessen* without definite effect — Typical myotonia and very slight muscle dystrophy with myopathic facies, indistinct speech, and weak hand-grasp Very slight mental changes and slight acrocyanosis Social conditions fairly good

106 Male, s, farm-hand, aged 25 *Dystrophia myotonica*

Myotonia from age of 15 Still works — Typical myotonia and slight muscle dystrophy with weak hand-grasp Very slight mental changes Atrophy of testes, and acrocyanosis Social conditions good

107 Female, s, domestic servant, aged 21 *Dystrophia myotonica*

Myotonia from age of 12 Typical myotonia in hands, no definite muscle dystrophy At examination 1946 ptosis No mental changes, slight acrocyanosis Social conditions good

108 Female, s, domestic servant aged 20 *Dystrophia myotonica*

Myotonia and muscle debilitation from age of about 14 — Her mother forbids examination Statement by her physician comparatively severe muscle dystrophy and severe mental changes Lives on her home

109 Female, s, domestic servant aged 22 *Dystrophia myotonica*

Weak of muscles and mentally debilitated from age of about 6 Has had no permanent work, unable to work after age of 18 — Typical myotonia and slight muscle dystrophy with myopathic facies nasal speech and weak hand-grasp Extremely severe mental changes I Q 66 per cent Very slight of build emaciated and miserable appearance Slight acrocyanosis Social conditions very bad, receives invalidity pension

110 Female, s, inmate mental hospital aged 18 *Dystrophia myotonica*

Muscle debilitation from age of about 6 Imbecile from earliest childhood confined to mental hospital since the age of 13 Here treated for tuberculosis — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies and nasal speech Imbecile with I Q 47 per cent Menstruation irregular Under care as mental defective

111 Female, s, inmate mental hospital aged 16 *Dystrophia myotonica*

Increasing muscle debilitation from before the age of 6 Imbecility from earliest childhood, admitted to mental hospital from her 11th year At the age of 3 her right foot was treated for talipes calcaneus and the left for paralytic talipes equinovarus — Typical myotonia and extremely severe universal muscle dystrophy with myopathic facies and nasal speech Utterly imbecile unable to keep occupied, mostly confined to bed Menstruation irregular Repulsive appearance, extremely emaciated Under care as mental defective

112 Boy, son of unskilled labourer, aged 8 Under observation for *dystrophia myotonica*

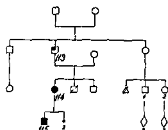
Slight of build lean with thin muscles mentally slightly debilitated No myotonia Suspected dystrophia myotonica Those among whom he lives have later stated the symptoms to have become more pronounced

Family No 10

This family has been followed through four generations to the family of a smallholder, b c. 1826 The family lived near Hillerod Zealand, and the first generation belonged to the level of small-holders and unskilled labourers Some members of the younger generations are artisans and one has married a teacher The family is of 29 persons, 18 of whom are living

One of those living has dystrophia myotonica and among the dead there is one supposed and one suspected case of the same affection

I happened to notice the propositus in the street as it was evident that he had dropfoot as well as myopathic facies



113 Male, m, unskilled labourer, d aged 32 *Suspected dystrophia myotonica.*
Walked with difficulty, Photograph shows myopathic facies

114 Female m to school principal, d aged 56 *Supposed dystrophia myotonica*
Atrophy in arms and legs,

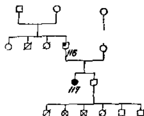
115 Male, s, tobacconist, aged 30
Myotonia stated not to ha

Family No 11.

The family has been followed through four generations to the family of a smallholder, b between 1820 and 1824 The family lived south of Hillerod, Zealand, two of the four children died in childhood, and it is impossible to trace the third The fourth child became a vagrant, and his two children were brought up by strangers and are now, respectively, an unskilled labourer and a domestic servant in bad social conditions The family investigation covers 16 persons of whom only 6 are living

One of these 6 has dystrophia myotonica, and the disease is suspected in one of the dead

The disease of the proposita was recognized by *Axel V Neel*



116. Male, m, unskilled labourer, d aged 59 *Suspected dystrophia myotonica*
Dromomania for many years Uncertain information pointing towards dystrophia myotonica

117 Fem

fror
abl

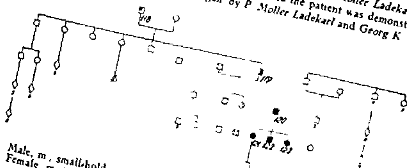
the legs Severe muscle dystrophy with myopathic facies, nasal speech, accentuated lumbar lordosis, and tendency to dropfoot Comparatively severe mental changes, moderate struma, cataract (s 1 e), and acrocyanosis Social conditions bad, receives invalidity pension

Family No 12

On the maternal side it is possible to follow the family of the propositus through four generations to the family of a small-holder b c 1524 living near Haderslev, North Slesvig, the descendants of whom all belonged to the category of unskilled labourers It was possible to follow the family through only two children of the first ancestors, the others having emigrated to the U S A about 1880 The paternity of the propositus is extremely doubtful, as the mother in her youth seems to have nourished fairly polygamous ideas The family of the putative father has been examined The present investigation comprises 66 persons 39 of whom are living

Four of the living have dystrophia myotonica and one cataract Dystrophia myotonica is suspected to have been present in one of the dead members

The disease of the propositus was recognized in 1938 by *P Möller Ladekarl* in the Eye Clinic of the Kommunehospital, Copenhagen and the patient was demonstrated in The Opthalmological Society Copenhagen by *P Möller Ladekarl* and *Georg K Sturup*



118 Male, m, small-holder d aged 40 *Suspected dystrophia myotonica*

119 Female m to unskilled labourer aged 82 *Cataract*
Senile nuclear cataract

120 Male, m, unskilled labourer aged 51 *Dystrophia myotonica, Propositus*
Myotonia and increasing loss of strength in hands from age of 34 Unfit to work from age of 42, manifest cataract from age of about 45 Despite operation, almost blind during later years Several times admitted to the Neurological Dept of the Kommunehospital, Copenhagen – Typical myotonia and extremely severe muscle dystrophy with myopathic facies Muscles of shoulders and upper arms almost completely paralytic arms hanging slack Only with the utmost difficulty was he able to carry his hand to his mouth Was wholly unable to help himself with the calls of nature Speech nasal and indistinct He had swallowing difficulties, and coughing was of a paralytic nature Difficulty in carrying his head on account of dystrophy of neck muscles he therefore balanced it in a slightly backward position Slight dropfoot Comparatively severe mental changes with intellectual deterioration and lack of initiative In spite of his miserable condition the patient was comparatively contented complacent, and had an exaggerated opinion of himself He was rather obese Testes and external genitalia atrophic In 24 hours' urine were found gonadotropin 375 R U (normal < 30) and testicular hormone 3 H U (normal 5—25) Frontal alopecia, pilosity otherwise normal. B M R 1938 73 per cent, 1942 54 per cent Serum cholesterol normal serum calcium normal, ecg normal with normal T-waves and P–Q = 20 sec B P 90 50 P 60 Cataract with residual cataract in operated left eye and stellate formation and

coloured grains in the posterior cortex of right eye Slight acrocyanosis Appearance utterly miserable, social conditions very bad Received invalidity pension Died in 1942 of bronchopneumonia, autopsy carried out.

121 Female, s, factory worker, aged 20 *Dystrophia myotonica, levissimo grado*
Slight myotonia in cold temperatures only, and objectively only mechanical myotonia in the right thenar and extensors of fore-arms No definite muscle dystrophy and very slight mental changes Cataract with speck-formed angular, white-grey opacities (s l e) Social conditions fairly good

122. Male, s, messenger, aged 19. *Dystrophia myotonica*
Myotonia ascertained at age of 15. Habitual jaw dislocation for several years Has had relatively badly paid work of a light nature — Typical myotonia and slight muscle dystrophy with myopathic facies and dystrophy of neck muscles Speech nasal and indistinct Comparatively severe mental changes, I Q 80 per cent, tires easily He lacks initiative and has an exaggerated opinion of himself [illegible] ocial conditions com-

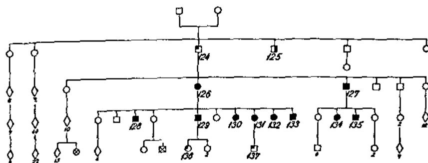
123 [illegible] *myotonica*
[illegible] nyotonica Increasing
[illegible] Moderate active myotonia in mastication muscles, and mechanical myotonia in tongue and extensors of fore-arms Only slight muscle dystrophy Sleeps with eyes open Comparatively severe mental changes, is backward

Family No 13.

The family has been followed through five generations to the family of a cowherd, b c 1820, living between Holbæk and Soro, Zealand Socially the majority of family members belong to the categories of small-holders or unskilled labourers, and many of the living are domiciled in the same district The investigations covers 182 persons, of whom 170 are living

Ten of the living have dystrophia myotonica, and 2 are suspected cases. One of the dead had cataract, and one is suspected to have had dystrophia myotonica

The propositus was found by this writer by investigation of the records of the Invalidity Insurance Court The patient had been admitted to the Neurological Department of the Rigshospital, Copenhagen, where the myotonia had been recognized



124. Male, m, cowherd, d aged 44 *Suspected dystrophia myotonica*

125 Male, m, unskilled labourer, d aged 74 *Cataract*

126 Female, m to journeyman miller, aged 64 *Dystrophia myotonica*
Cataract from age of 57. Hands always hypersensitive to cold — Slight, typical myotonia and very slight muscle dystrophy in face and neck Mentally natural Very thin-haired Cataract and slight acrocyanosis Social conditions comparatively bad, receives old age pension

127 Male, m., small-holder, aged 61 *Dystrophia myotonica*

Myotonia from age of 53, and growing cataract from age of 51 — Typical myotonia and very slight muscle dystrophy with myopathic facies. Mentally natural Alopecia and cataract Social conditions fairly good, owns his own small-holding

128 Male, s., unskilled labourer, aged 39 *Dystrophia myotonica Propositus*

Myotonia from age of 8, and increasing weakening of muscles from age of 14 Unable to work from age of 31 — Typical myotonia, spread to the legs Comparatively slight muscle dystrophy with myopathic facies and slight dropfoot Comparatively severe mental changes atrophy of testes alopecia, cataract and acrocyanosis Appearance miserable and pitiable Social conditions bad, receives invalidity pension

129 Male, m., unskilled labourer aged 35 *Dystrophia myotonica*

Myotonia from age of 10 Sentenced for receiving Examined in State prison Typical myotonia and very slight muscle dystrophy with myopathic facies and slight nasal speech Moderate mental changes Slight atrophy of testes and alopecia Is able to work, but social conditions are but fairly good

130 Female, m., to unskilled labourer, aged 31 *Dystrophia myotonica*

Increasing myotonia and increasing universal weakening of strength from age of 14 Treated for neurasthenia in local hospitals — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies and weak hand-grasp Severe mental changes, which mark her home as well as her own appearance Is completely devoid of initiative and appears depressed Rather corpulent Medium-sized, comparatively soft struma without pulsation Irregular hypermenorrhea Hands cold and clammy Looks miserable slack and pitiable Social conditions extremely bad

131 Female, m to unskilled labourer aged 29 *Dystrophia myotonica*

Myotonia from age of 10 and increasing reduction of strength with advancing years Hands hypersensitive to cold — Comparatively severe and extensive myotonia, and comparatively moderate muscle dystrophy with myopathic facies, head drooping forward, and tendency to dropfoot Comparatively moderate mental changes. Incipient alopecia and acrocyanosis Able to look after her home social conditions fairly good

132 Female, s and unemployed aged 25 *Dystrophia myotonica*

Imbecile from early childhood, myotonia and hypersensitivity to cold from age af about 10 Has never worked — Typical myotonia and slight muscle dystrophy with myopathic facies and nasal speech Is imbecile and obese Hyper-menorrhea Lives on special municipal grants

133 Male, s., unskilled labourer, aged 22 *Dystrophia myotonica*

Myotonia from age of 8, especially troublesome in cold No permanent work At present lives on casual work at low wages Typical myotonia and very slight muscle dystrophy Severe mental changes atrophy of testes and acrocya-nosis Bad social conditions lives on his mother

134 Female s., domestic servant aged 26 *Dystrophia myotonica*

Myotonia from age of 23 — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies forward-drooping head and accentuated lum-lordosis Only slight mental changes Manages work without difficulty Social conditions comparatively good

135. Male, s., farm-hand, aged 24 *Dystrophia myotonica*

Myotonia from age of 22 but photograph from 8th year reveals defini myopathic facies Difficult to wake up in the morning — Typical myotonia an slight muscle dystrophy with myopathic facies Comparatively slight menta changes Atrophy of testes and incipient alopecia Manages work, social conditions comparatively good

136 Girl, daughter of unskilled labourer aged 10 *Under observation for dystrophia myotonica* Mechanical myotonia in tongue and incipient myopathic facies (Examination when 14 showed typical dystrophia myotonica.)

137 Girl, daughter of unskilled labourer, aged 4 *Under observation for dystrophia myotonica*

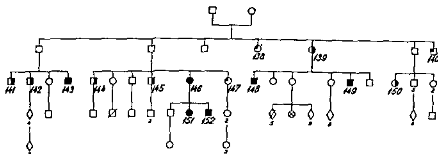
States symptoms of active myotonia, no definite muscle dystrophy Examina-tion for mechanichal myotonia rendered impossible by the child's refusal

Family No. 14.

This family was followed through five generations to the family of a sailor, b 1816—1820, living in Copenhagen His descendants are mainly artisans, living in or near Copenhagen The investigation covers 84 persons, 67 of whom are living

Among those living 4 have dystrophia myotonica and 3 cataract Among the dead there were 2 supposed and 5 suspected cases of dystrophia myotonica, and one with cataract

The disease of the propositus was recognized by *Eigil Hess Thaysen* in the Hospital of the Sisters of St Elizabeth, Copenhagen



138 Female, d aged 52 *Suspected dystrophia myotonica*
Died in a nursing home

139 Female, m to a sailor, d aged 71 *Cataract, suspected dystrophia myotonica*

140 Male, s, d at unknown age *Suspected dystrophia myotonica*
Died in a nursing home

141 Male, m, master painter, aged 68 *Cataract*
Pronounced cerulean cataract and, besides, in the anterior and posterior cortex, greyish spots and radial feather-like blurring (s l e)

142 Male, m, glazier, aged 66 *Cataract*
Cerulean cataract with irregular greyish opacities in cortex and nucleus Radial blurring in anterior and posterior cortex (s l e)

143

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[illegible] severe muscle dystrophy with myopathic facies, nasal speech, swallowing trouble, habitual jaw dislocation, very weak strength in hands, and dropfoot Comparatively severe mental changes The patient is rather obese, testes and external genitalia atrophic Alopecia, and cataract with diffuse and spotty, partly radial

opacities Ecg. broad initial complexes P—Q 24 sec Appearance miserable, social conditions extremely bad Draws regular sick benefits

150 Female, s, housekeeper, aged 58 *Cataract*

151 Female, s, clerk, aged 31 *Dystrophia myotonica*

Myotonia from age of 14 Always weak strength of hands. — Comparatively widespread myotonia with difficulty in taking initial steps Slight muscle dystrophy Mentally natural Menstruation irregular, slight acrocyanosis Social conditions good

152 Male, s, former printer, aged 28 *Dystrophia myotonica*

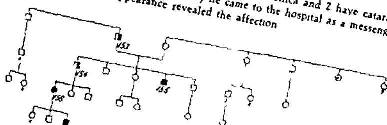
Myotonia from age of 18, and increasing muscle debilitation from age of 22 when the patient was treated for tuberculosis of lungs and genitalia — Typical myotonia and severe muscle dystrophy with myopathic facies and dropfoot Severe mental changes Atrophy of testes, alopecia, and acrocyanosis Cataract with speckformed and radial opacities in anterior and posterior cortex (s l c) Lives on his parents and receives invalidity pension

Family No 15

This family can be traced back to two brothers, b 1852 and 1860 near Rodby, Isle of Lolland The one was a farmer in that district the other became a railway official The greater part of the living members live in or near Copenhagen The social standard has been retained, the descendants being artisans, grocers and waiters The investigation covers 40 persons, 36 of whom are living

Three of the living members have dystrophia myotonica and 2 have cataract

I noticed the propositus when one day he came to the hospital as a messenger from a florist's shop and his appearance revealed the affection



153 Male, m, former railway official aged 82 *Cataract*

154 Male, m, hall-porter, aged 55 *Cataract*

155 Male, s, messenger, aged 42 *Dystrophia myotonica Propositus*

Myotonia from age of 35, during later years decreasing strength Mental debilitation from childhood Was sent from home because he was considered lazy Vainly applied for invalidity pension — Typical myotonia and comparatively slight muscle dystrophy with myopathic facies Severe mental changes I Q 75 per cent Atrophy of testes and external genitalia Alopecia and acrocyanosis Appearance miserable and pitiable Social conditions bad, has a small income as a messenger, and now receives invalidity pension

156 Female, m to mechanic, aged 30 *Dystrophia myotonica*

Myotonia from age of 14 Has always been very tired — Typical myotonia and slight muscle dystrophy with myopathic facies and nasal speech Hand-grasp comparatively weak Fairly severe mental changes with lack of initiative, evident from appearance of home Slight acrocyanosis Has a large family of children and lives in comparatively bad social conditions

157 Boy son of mechanic, aged 2 *Dystrophia myotonica*

Imbecility from birth and congenital talipes valgus Mechanical myotonia No elective muscle dystrophy, but all muscles are thin At the age of 4 he also presented active myotonia.

Family No. 16.

The family was followed through four generations to a family of unskilled labourers near Holbæk, Zealand Their descendants are small-holders, unskilled labourers, or artisans They nearly all live in the same district as the first generation The investigation covers 35 persons, 31 of whom are living.

Three of the living have dystrophia myotonica and one has cataract

I found the propositus by attending the rounds in the Ebberodgaard Hospital for Mental Defectives Here the patient was only diagnosed imbecile

The investigation of this family has not been carried out so thoroughly as desired because of difficult travelling conditions

158. Male, m , master carpenter, aged 63 *Cataract* (statement by his physician)

159

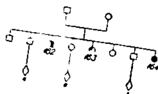
160

161 tongue, and me- nasal, otherwise er-nourished

Family No 17.

The family can be followed through three generations to the family of a small-holder, b c 1860 His descendants are unskilled labourers or small-holders, and live in the same region, north-west of Norre-Sundby, Jutland The investigation covers 25 persons, 21 of whom are living, but it has not been so thorough as desired because of difficult travelling conditions The information collected partly originates from practitioners and from the family members themselves.

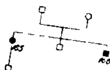
Only one of the living members has dystrophia myotonica. Two of the dead are suspected of having had the same affection, one of them, further, having cataract.
The disease of the proposita was recognized in the Neurological Department of the Rigshospital, Copenhagen



162 Male, s, unskilled labourer d aged 35 *Cataract suspected dystrophia myotonica*
163 Female, s, domestic servant, d aged 29 *Suspected dystrophia myotonica*
164 Female, s, domestic servant aged 33 *Dystrophia myotonica Proposita*
Myotonia and increasing muscle debilitation from age of 14 Has never been able to work away from home — Typical myotonia and comparatively severe muscle dystrophy with myopathic facies nasal and hoarse speech Comparatively severe mental changes, especially complete absence of initiative Irregular hypermenorrhea, incipient alopecia and acrocyanosis Laryngoscopy failing occlusion at intonation Subcortical spotty cataract (s l e) Has lived on her family in very bad social conditions, now receives invalidity pension

Family No 18

The family is followed through only three generations on account of travelling difficulties It descends from the family of a market-gardener, b c 1890, living in Viborg, Jutland Two of its six members, all of whom are living have dystrophia myotonica The mother has been examined for cataract but it has been impossible to subject the father to slit lamp examination
The disease of the propositus was recognized by *Georg K Stürup* in the Orthopedic Hospital, Copenhagen



165 Female, divorced shop-assistant aged 27 *Dystrophia myotonica*
Myotonia from age of 22 and increasing muscle debilitation during later years The husband divorced her on account of her changed mentality — she grew untidy and indolent, the child was not properly looked after and the home deteriorated — Typical, comparatively severe myotonia also in legs Myopathic facies nasal speech and dystrophy of neck muscles otherwise no muscle dystrophy Comparatively severe mental changes as described She is obese Menstruation irregular, very vehement Slight acrocyanosis Cataract with fine coloured grains in anterior and posterior cortex (s l e) Appearance marked by her lack of initiative and disorderliness Social conditions still fairly good
166 Male, s, plumber's apprentice aged 16 *Dystrophia myotonica Propositus*
Increasing myotonia from age of 12 hampering his work, especially in cold — Typical and severe myotonia and myopathic facies nasal and indistinct speech

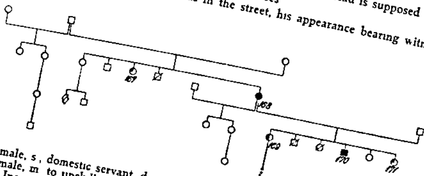
Otherwise only suggestions of muscle dystrophy. Mentally natural Acrocyano. Has with good effect been treated with quinine, 25 cg 4 to 6 times daily for perio of one week with intermittent intervals of one week. Social conditions fairly goo

Family No. 19.

This family was followed through four generations back to a tobacco-worker family, the husband of which was born in 1827 in Randers, the wife in 1837 north-east of Horsens, both in Jutland The greater part of their descendants live in or near Copenhagen, and the majority were and are unskilled labourers The investigation comprises 25 persons, 9 of whom are living

Of those living, 2 have dystrophia myotonica One of the dead is supposed to have had dystrophia myotonica, and 2 are suspected cases

I happened to spot the propositus in the street, his appearance bearing witness to his affection



167 Female, s, domestic servant, d aged 20 *Suspected dystrophia myotonica*
168 Female, m to unskilled labourer, aged 67 *Dystrophia myotonica*
Increasing cataract from age of 54, operated on — Very slight active and mechanical myotonia, no definite muscle dystrophy Slight mental changes Obese with incipient alopecia After-effects of cataract operation Lives on old age pension in comparatively bad social conditions
169 Female, m to unskilled labourer, d aged 25 *Supposed dystrophia myotonica*
170 Male, s, messenger, aged 31 *Dystrophia myotonica Propositus*
Myotonia and increasing muscle debilitation from age of 14 Mentally debilitated from childhood, after school age he has had only light work at very low wages — Typical myotonia and comparatively severe muscle dystrophy with myopathic facies, nasal speech, weak strength in hands and arms Comparatively severe mental changes Atrophy of testes and external genitalia Frontal alopecia, hands blue and cold Extremely emaciated, appearance miserable Social conditions bad
171 Girl, daughter of unskilled labourer, d aged 13 *Suspected dystrophia myotonica*

Family No. 20.

The family was followed through four generations to a clergymann's family, living near Varde, Jutland Both husband and wife descend from well-known Danish clerical families, and their descendants were and are university men, prominent farmers, or business men They live fairly scattered over Denmark Difficult travelling conditions have rendered this investigation less thorough than desired In many cases I have had either to ask the family member in question or the local practitioner The investigation comprises 56 persons, 41 or whom are living Of these, one has dystrophia myotonica,

one is a supposed case, and one has cataract Among the dead there is one suspected case of dystrophia myotonica, and one had cataract

The disease of the proposita was recognized by *Haagen Jessen*, Aarhus.

172 *Female, s., music teacher, d aged 78 Cataract*

173 [illegible]

174 [illegible]

175 [illegible] who [illegible] onica

176 [illegible] from [illegible] her household tasks — Typic[illegible] y slight muscle dystrophy with myopa[illegible] ruation B M R 99 and 94 per cent [illegible] (s l e.) Cortiron treatment, 10 mg × [illegible] 10 lbs in weight Social conditions good

Family No 21

The family has been followed through four generations to the family of an unskilled labourer b c 1846 near Elsinore *His descendants are unskilled labourers*, small-holder, or lesser business people and a few are clerks A number has emigrated *to the U S A The investigation covers 61 persons, 47 of whom are living and* domiciled in this country

Among those living, 2 have dystrophia myotonica, and among the dead or emigrated there are 2 suspected cases of the disease and one has cataract

The disease of the propositus was recognized in the Neurological Department of the Rigshospital Copenhagen

177. Female m to unskilled labourer d aged 85 *Cataract*

178 Female, m to a pork-butcher d aged 45 *Suspected dystrophia myotonica*

179 Male m former unskilled labourer aged 45 *Dystrophia myotonica*

Increasing muscle debilitation especially in arms from age of 20 Unfit to

work from age of 28, and cataract from age of 46 Investigated in medical special department — there diagnosed progressive muscular dystrophy, atrophy of both testes — Typical myotonia and very severe muscle dystrophy with myopathic facies and very weak arm muscles Comparatively severe mental changes, satisfactory state of nutrition, atrophy of testes and external genitalia, alopecia, and cataract The home is virtually maintained by his diligent wife Social conditions bad; receives invalidity pension

180 Female, aged about 42, domiciled in the U S A *Suspected dystrophia myotonica*

181 Male, s, former unskilled labourer, aged 46 *Dystrophia myotonica Propositus.*

Increasing muscle debilitation in hands from age of 34, myotonia from 44 Mentally debilitated from childhood, unfit to work from age of 40 — Extensive myoton[illegible] dystrophy with myopathic facies, [illegible] ecurvated knees, and drop-foot S[illegible] ely severe mental changes with la[illegible] nutrition, B M R 81—83 per cer[illegible] I-II almost iso-electric; T_{III} negative [illegible] degeneration) Serum calcium and phosphorus normal. Creatine in 24 hours' urine 38—56 mg Laryngoscopy no abnormalities. Pharyngeal hypersecretion Cataract with small glittering subcapsular opacities (s l. e) Miserable appearance and very bad social conditions Received invalidity pension from his 44th year

Killed 1944 by anti-aircraft-shells, autopsy carried out

RESUMÉ

Kapitel I

(Indledning)

Myotoni blev først beskrevet som specifikt symptom i 1876 af lægen Asmus Julius Thomas Thomsen, som selv havde myotoni.

Myotoni er det karakteristiske symptom ved de arvelige sygdomme Thomsens sygdom (myotonia congenita), paramyotonia og dystrophia myotonica. Disse sygdomme er ikke sjældne og især ikke dystrophia myotonica. Der har været en del diskussion om berettigelsen af at betragte dem som nosologiske enheder. Dette problem har baade teoretisk interesse og praktisk betydning med henblik paa arvehygiejnen.

Kapitel II

Symptomet myotoni viser sig ved uvilkaarlig forlængelse af kontraktion i tværstribet muskulatur som følge af vilkaarlig innervation (aktiv myotoni), mekanisk irritation (mekanisk myotoni) eller elektrisk irritation af musklen (elektrisk myotoni). Den forlængede kontraktion er ledsaget af karakteristisk elektrisk aktivitet i musklen.

Ved Thomsens sygdom (og paramyotonia) er myotonien oftest meget udbredt og manifesterer sig i den tidlige barnealder. Ved dystrophia myotonica er den derimod som regel lokaliseret til enkelte muskelgrupper (underarms- og tyggemuskler) og manifesterer sig meget sjældent før 6 aars alderen og hyppigst mellem 15 og 20 aar.

De helt afslappede myotone muskler har normal konsistens, og tonus. Myotonien afhænger til en vis grad af kraftudfoldelsen og svinder ved gentagelse af kontraktionen. I de fleste tilfælde føles funktionshæmningen stærkest i kulde, selvom myotonien egentlig er kortvarigere. Træthed og psykisk paavirkning, menstruation og graviditet kan forværre myotonien. Ved svære grader kan patienten ved forskrækkelse blive statuestiv i ca. 1 minut.

Ved Thomsens sygdom kan myotonien tilsyneladende blive mindre generende med alderen. Ved dystrophia myotonica svinder myotonien med indtrædende muskeldystrofi.

Mekanisk myotoni maa ikke forveksles med den idiomuskulære reaktion, som er en lokal fremhvælvning, medens den mekaniske myotoni oftest viser sig ved en fure i musklens overflade svarende til det kontraherede muskelbundt. Den er udbredt omtrent svarende til den aktive myotoni og paavises særlig tydeligt i tungerand, underarmsextensorer og thenar. Elektrisk myotoni er ikke undersøgt i dette arbejde

Myotoni er konstateret i en gedestamme fra Tenessee i U. S. A. Disse dyr er blevet anvendt til pathofysiologiske og farmakologiske experimenter.

Elektromyografi med concentriske naalelektroder er en særdeles vigtig undersøgelse ved myotoni Myotonien er ledsaget af en karakteristisk elektrisk aktivitet, og i hvile kan som regel paavises en typisk aktivitet

Den myotone elektriske aktivitet opstaar efter alt at dømme i muskelpladen, som maa være abnorm følsom, idet den reagerer paa vilkaarlig impuls og mekanisk eller elektrisk irritament med en serie og ikke een enkelt udladning som i normale muskler. Denne aktivitet forsvinder ved lokal applikation af novocain ½ % og ved behandling med kinin lokalt eller universelt

Der er ikke paavist forskel paa myotonien hos patienter med Thomsens sygdom og dystrophia myotonica.

Myotonien kan bringes til at svinde delvis eller helt ved behandling med kinin pr os i store doser (1—1,75 gram daglig). Virkningen er kortvarig og accentueres af calcium i store doser. Der er tilvænning, og af denne grund gives kinin i 8 dage ad gangen med 8 dages interval Behandlingen er som regel kun indiceret ved Thomsens sygdom, sjældent ved dystrophia myotonica.

Kapitel III.

Ved *Thomsens sygdom* er der kun muskulære symptomer. En som

muskulære dystrofier, og patienternes sociale niveau paavirkes ikke af sygdommen. Ingen af mine 29 patienter behøver hjælp paa grund af Thomsens sygdom

Sygdommen er langtfra saa hyppig som dystrophia myotonica. Den er beskrevet i mange lande i Europa, i U S. A og i Japan, og der er ingen paaviselig forbindelse mellem de beskrevne slægter. Den er lige hyppig hos de to køn, men probanderne er hyppigst hos mænd Den manifesterer sig oftest i den tidlige barnealder og er i nogle tilfælde til stede i spædbarnsalderen Den er hereditær. I dr. Thomsens slægt og en række andre slægter arves den med simpel dominans med stærk penetrans, men i andre

slægter arves den formentlig paa dominant maade med varierende manifestation. Muligheden for recessiv hereditet i visse slægter kan ikke sikkert udelukkes.

Sygdommens klinik og arvebiologi er i dette arbejde belyst ved undersøgelse af 5 danske slægter (deriblandt en gren af dr. Thomsens slægt) med ialt 29 levende patienter.

Kapitel IV

Paramyotoni viser sig ved spontan, tonisk kontraktion i tværstribede muskler efterfulgt af mere eller mindre udtalt parese som følge af kuldepaavirkning. Der er en jævn overgang fra kuldefænomenerne ved den beskrevne myotoni til paramyotonien, og da der praktisk talt altid er muskelhypertrofi hos patienter med paramyotoni, anses syndromet for at være en speciel variant af Thomsens sygdom Herediteten er dominant

Der er ingen patienter med paramyotonia i mit materiale

Kapitel V.

Ved en kritisk litterær analyse paavises, at diagnosen *myotonia acquisita* sandsynligvis ikke har nogen berettigelse.

Kapitel VI

Hos patienter med *myxødem* er der i visse tilfælde muskelhypertrofi og træg muskelfunktion (*Debré-Semelaignes* syndrom) og i nogle tilfælde tillige en myotonilignende funktionsforstyrrelse (*Hoffmanns* syndrom) Dette sidste syndrom er ofte blevet beskrevet som Thomsens sygdom Undersøgelse af en patient med dette syndrom har vist, at der ikke er tale om myotoni. Baade muskelhypertrofi og de myotonoide funktionsforstyrrelser svandt sammen med myxødemet ved behandling med thyreodin

Kapitel VII

Dystrophia myotonica er først og fremmest præget af dystrofiske symptomer, dels muskulære, dels extramuskulære. Myotonien er oftest lokaliseret til enkelte, symmetriske muskelgrupper Muskeldystrofien rammer fortrinsvis ansigts-, tygge-, tunge-, hals- og underarmsmuskler, men kan efterhaanden blive meget udbredt Der er ingen karakteristiske forandringer i kreatin-kreatininudskillelsen i urinen. Reflexsvækkelse er reglen i dystrofiske, men kan ogsaa konstateres i ikke dystrofiske musk-

ler. I sjældne Tilfælde er der fundet let hypæsthesi og hypalgesi distalt paa extremiteterne, og der er konstateret svækket vibrationssans hos en række patienter med dystrophia myotonica (*Maas*)

Katarakt findes ofte som solitært symptom hos forældre, og hos 87 % af mine patienter var der linseuklarheder, som i de fleste tilfælde havde et ret karakteristisk udseende (myotonikatarakt). Moden katarakt udvikles sjældent før 45 aars alderen. Ptose, lagophthalmus og blepharoconjunctivitis skyldes muskeldystrofien, men den ret konstant forekommende enophthalmus har maaske endocrin aarsag.

Gonadedystrofi fandtes hos 86 % af mændene og antagelig hos 64 % af kvinderne, som havde menstruationsforstyrrelser Der var hos de fleste nedsat udskillelse af testishormon, oestrin og nedsat libido og potentia sexualis

Basalstofskiftenedsættelse uden myxodemsymptomer fandtes hos mange patienter. I glandula thyreoidea var der oftest colloide forandringer

Der fandtes ingen tydelige forandringer i pancreas's interne sekretion, selv om blodsukkeret ofte var lidt lavt

Klinisk er der ikke sikre holdepunkter for dystrofi af binyrebarken. Histologisk kan paavises dystrofi med fibrose af binyrebarken og ved forsøg paa substitutionsterapi er der i flere tilfælde fundet en tydelig subjektiv bedring af træthed.

Glandulae parathyreoideaes funktion var tilsyneladende normal

Det kliniske billede ved dystrophia myotonica har visse lighedspunkter med et kronisk Simmonds syndrom, og selvom der ikke ved den histologiske undersøgelse endnu er konstateret sikre forandringer, er det dog sandsynligst, at det brogede kliniske billede kan henføres til funktionsforstyrrelse i hypothalamus-hypofysesystemet

Frontoparietal skaldethed giver sammen med det typiske facies myopatica et karakteristisk udseende Skaldethed fandtes hos 83 % af mændene, men kun hos 16 % af kvinderne.

Vasomotoriske forstyrrelser med acrocyanose og vasospasmer var til stede hos $^2/_3$ af patienterne, og i nogle tilfælde var der forlænget overledningstid ved elektrocardiografi Der er beskrevet forbigaaende hjerteblok, og mange patienter har en let bradycardi

Deformering af ansigtsskelettet med høj gane og adenoidt habitus er et meget hyppigt forekommende symptom Fremadludende hoved, accentuerede rygkrumninger, recurvation af knæene og spidsfod er meget almindelig. I enkelte tilfælde er der paavist fortykkelse af teca cranii og hyperostosis frontalis int

Psykiske forandringer er et meget vigtigt symptom. Der er betydelig intelligensnedsættelse hos ⅓ og initiativsvækkelse hos $^3/_5$ af patienterne i den arbejdsdygtige alder. Flere er paa asyl for aandssvage. De psykiske

forandringer virker i mange tilfælde hæmmende paa den i forvejen nedsatte arbejdsevne.

Hos patienter med dystrophia myotonica er der næsten konstant en tydelig social deroute. 61,5 % af patienterne mellem 15 og 60 aar har en arbejdsevne, som er mindre end ⅓, og mange af dem faar invaliderente

Sygdommen er udbredt i Europa, i U S. A, Sydamerika og Japan og forekommer langt hyppigere end Thomsens sygdom Den er lige hyppig hos de to køn, men muskeldystrofien er sædvanligvis sværest hos mænd ligesom den sociale tilbagegang. Sygdommen manifesterer sig gennemsnitlig i 19 aars alderen, og ved sen manifestation er symptomerne ofte svage. De fleste dør inden 50 aars alderen

Den effektive fertilitet er nedsat, og der er paafaldende mange ugifte blandt patienterne. Sygdommen arves paa dominant maade med varierende, ikke svigtende manifestation Visse forhold taler for, at herediteten er progressiv endende med ikke forplantningsdygtige, syge individer, men det er muligt, at progressionen skyldes udvælgelse i forældregenerationerne. Fraternel degeneration fandtes ikke i mine slægter Undersøgelsen omfatter 21 slægter med 101 levende patienter

Kapitel VIII

Den kliniske undersøgelse har vist, at Thomsens sygdom (og paramyotonia) er væsensforskellige fra dystrophia myotonica Ved slægtsundersøgelsen er der ikke fundet holdepunkter for det i litteraturen fremsatte postulat, at disse sygdomme genetisk er identiske

Erkendelsen af myotonisymptomet letter differentialdiagnosen overfor en række muskelsygdomme og sygdomme med symptomer svarende til de extramuskulære dystrofiske forandringer ved dystrophia myotonica Et haandtryk er ofte tilstrækkeligt til at afsløre den rette diagnose

Kapitel IX

Myotonisymptomet kan som beskrevet behandles med kinin i store doser, med denne behandling er i reglen kun indiceret hos patienter med Thomsens sygdom.

En virkelig effektiv terapi ved dystrophia myotonica kendes ikke, men desoxycorticosteronacetat kan i visse tilfælde bedre asthenien, som generer mange af disse patienter E-vitamin i store doser kan maaske hæmme udviklingen af muskeldystrofien, men hidtil er der kun konstateret subjectiv bedring

Ved at erkende sygdommen kan man dog hjælpe mange af disse patienter, idet det derigennem bliver muligt at skaffe dem den nødvendige hjælp gennem den sociale forsorg.

Kapitel X.

Arvehygiejniske foranstaltninger kommer kun paa tale, naar det drejer sig om dystrophia myotonica Thomsens sygdom (og paramyotonia) er nok generende, men virker sjældent invaliderende. Hos patienter og sikre anlægsbærere med dystrophia myotonica vil man først fraraade at sætte børn i verden og belære dem om metoderne hertil. Saafremt dette er ineffektivt, kan der blive tale om sterilisation og eventuelt abortus provocatus paa eugenisk indikation.

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Kapitel X.

Arvehygiejniske foranstaltninger kommer kun paa tale, naar det drejer sig om dystrophia myotonica. Thomsens sygdom (og paramyotonia) er nok generende, men virker sjældent invaliderende. Hos patienter og sikre anlægsbærere med dystrophia myotonica vil man først fraraade at sætte børn i verden og belære dem om metoderne hertil. Saafremt dette er ineffektivt, kan der blive tale om sterilisation og eventuelt abortus provocatus paa eugenisk indikation.

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